Predicting Clinical Outcome in Children with ADHD

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Is there a Role for Neurocognitive Functioning?

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Predicting Clinical Outcome in Children with ADHD

Is there a Role for Neurocognitive Functioning?

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CHAPTER 1

General Introduction

Prologue

Attention-Deficit/Hyperactivity Disorder, or ADHD, is a disorder that is subject to intense debate in both the scientific field and in society. This thesis is written to increase our scientific knowledge of the course of ADHD and the role of neurocognitive functioning therein. It is an attempt to unravel the underlying etiological mechanisms of ADHD using longitudinal information on behavioral and neurocognitive factors. Such information could, for example, increase the validity of the prognosis of the disorder, thereby providing input on psychoeducation to individuals with ADHD and their families, and may potentially guide treatment planning. Regarding the societal debate, this thesis aims to provide a reliable and objective representation regarding the course of ADHD, with its careful and extensive diagnostic procedures over time.

Both a descriptive as well as a predictive perspective are taken as (a) both the course of ADHD symptoms (symptom change and persistence rates) and the course of neurocognitive functioning are investigated in **Chapter 3 and 5**, and (b) ADHD outcomes (ADHD symptom severity and symptom change, overall functioning, comorbid problems) are predicted from behavioral and neurocognitive characteristics, using baseline (**Chapter 2, 3 and 4**) and longitudinal information (**Chapter 2, 5 and 6**). See Figure 1.1 for a visual outline of this thesis.

This first chapter serves as an introduction to ADHD and its course, followed more specifically by a discussion of the role of neurocognitive functioning in ADHD and of theories that may explain the relationship between neurocognitive functioning and ADHD behavior. Finally, advances of the current study, together with a description of the study design and specific aims will be described.

Attention-Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder is a common developmental disorder, affecting around 5% of children and adolescents (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014) and 2.5% of adults (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). Prevalence rates of ADHD overall are higher in males compared to females, although females had higher inattentive symptom presentations compared to males (Willcutt, 2012). ADHD is characterized by symptoms of inattention and/or hyperactivity/ impulsivity and is associated with functional impairments in multiple domains of functioning, described as such in both the Diagnostic and Statistical Manual of mental disorders (DSM)-IV and DSM-5 (American Psychiatric Association, 2000; American Psychiatric Association, 2013; see Box 1.1). Diagnostic criteria for ADHD have changed with the introduction of the DSM-5, which replaced the DSM-IV. Specifically, DSM-5 requires

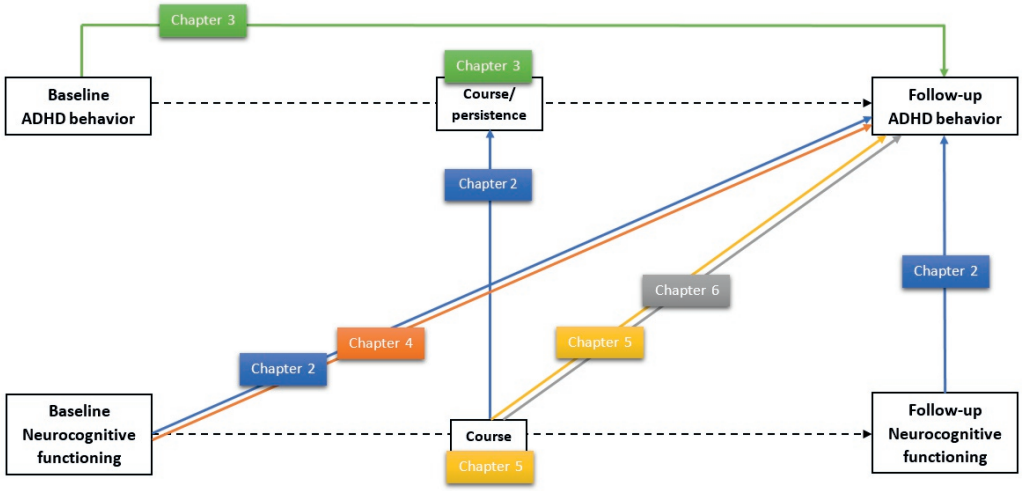

Figure 1.1. Visual outline of this thesis. Colored lines indicate the relationships between predictor(s) and outcome(s) that are investigated in this thesis. Chapter 2 is a systematic review of the literature, other Chapters contain data from the IMAGE and NeuroIMAGE sample. Chapter 3 also includes ADHD related predictive factors such as ADHD familiality, comorbidities, treatment. ADHD = Attention-Deficit/Hyperactivity Disorder; IMAGE = International Multicenter ADHD Genetics.

an age of onset of 12 years, five symptoms per symptom axis for individuals of 17 years and older, and presence of an autism spectrum disorder is allowed, whereas DSM-IV defined an age of onset of 7 years, six symptoms per symptom axis for individuals of 17 years and older, and finally, ADHD was not allowed to be diagnosed in the presence of an autism spectrum disorder. Importantly, ADHD symptoms are continuously distributed in the population. Individuals on the extreme end are likely to have a diagnosis (Asherson & Trzaskowski, 2015; Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012).

Impairment exists in several domains of functioning, including academic, social, and occupation functioning (Barkley, Fischer, Smallish, & Fletcher, 2006; Hoza, 2007; Loe & Feldman, 2007). In addition, the majority of individuals with ADHD has at least one comorbid DSM-diagnosis, most frequently reported comorbidities are externalizing disorders (e.g. oppositional defiant disorder [ODD], or conduct disorder [CD], 50-60%), internalizing disorders (e.g. depression [16-26%], anxiety [12%]). Although ADHD and autism spectrum disorders were not allowed to be diagnosed together, in 60-85% of the children with ADHD symptoms of autism spectrum disorders are apparent (Gillberg et al., 2004). Several studies have shown genetic

BOX 1.1 DSM-5 criteria for Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2):
(1) Six or more symptoms of *inattention* for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level:

Inattention
a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.
b. Often has trouble holding attention on tasks or play activities.
c. Often does not seem to listen when spoken to directly.
d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).
e. Often has trouble organizing tasks and activities.
f. Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).
g. Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
h. Is often easily distracted.
i. Is often forgetful in daily activities.

(2) Six or more symptoms of *hyperactivity-impulsivity* for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level:

Hyperactivity
a. Often fidgets with or taps hands or feet, or squirms in seat.
b. Often leaves seat in situations when remaining seated is expected.
c. Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
d. Often unable to play or take part in leisure activities quietly.
e. Is often "on the go" acting as if "driven by a motor".
f. Often talks excessively.

Impulsivity
g. Often blurts out an answer before a question has been completed.
h. Often has trouble waiting his/her turn.
i. Often interrupts or intrudes on others (e.g., butts into conversations or games).

In addition, the following conditions must be met:
B. Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.
C. Several symptoms are present in two or more setting, (e.g., at home, school or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.
E. The symptoms do not happen only during the course of schizophrenia or another psychotic disorder. The symptoms are not better explained by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Based on the types of symptoms, three kinds (presentations) of ADHD can occur:
- *Combined Presentation*: If enough symptoms of both criteria inattention and hyperactivity-impulsivity were present for the past six months.
- *Predominantly Inattentive Presentation*: If enough symptoms of inattention, but not hyperactivity-impulsivity, were present for the past six months
- *Predominantly Hyperactive-Impulsive Presentation*: If enough symptoms of hyperactivity-impulsivity but not inattention were present for the past six months.

associations between comorbid problems (e.g. mood and emotional self-regulation, conduct disorder) and ADHD (see Faraone et al., 2015), confirming existing associations among behavioral problems.

The decrease in prevalence from ADHD in childhood to ADHD in adulthood implies an age-related symptom decline. A meta-analysis on retention of ADHD over time showed that, starting at age nine, every five years the rate of ADHD declines by 50% (Hill & Schoener, 1996). This is particularly true for symptoms of hyperactivity/impulsivity, but much less so for symptoms of inattention, which are relatively stable with advancing age (Biederman, Mick, & Faraone, 2000; Hart, Lahey, Loeber, Applegate, & Frick, 1995). When applying strict versus loose definitions of persistence (i.e. meeting full diagnostic criteria for ADHD according to the DSM-IV (American Psychiatric Association, 1994) versus meeting DSM-IV ADHD in partial remission criteria), 15% versus 65% of children remain symptomatic at age 25 (Faraone, Biederman, & Mick, 2006). A later study showed that even 70% of children with a childhood diagnosis of ADHD continued to meet full ADHD DSM-IV criteria in adolescence (Langley et al., 2010). These data thus show that large proportions of children have persistent and impairing symptoms of ADHD in young adulthood (see for a review also Faraone et al., 2015). This is confirmed by findings indicating that persistent ADHD is associated with experiencing chronic problems in adult life compared to those with remitted ADHD, such as higher rates of substance use disorders (Klein et al., 2012) and other psychiatric comorbidities (Barbaresi et al., 2013). However, individuals with remittent ADHD also were impaired in adult life, for example on their level of social functioning. On the other hand, they were not clearly impaired on occupational functioning (Klein et al., 2012).

Genes, Environment, and the Brain

With an estimated heritability rate of 76 percent in twin studies (Faraone et al., 2005) it is suggested that genetic factors play an important role in ADHD. It is now known that both stable genetic factors are involved in the onset of ADHD, as well as that there are genes contributing at different developmental stages, probably relating to a persistent or remittent course of ADHD (Chang, Lichtenstein, Asherson, & Larsson, 2013; Pingault et al., 2015). Importantly, it is likely that the onset and/or course of ADHD is dependent on (interactions between) multiple genetic factors with a small effect each (Faraone et al., 2005). On the environmental level, extreme early adversity (e.g. extreme early deprivation), pre- and postnatal exposure to lead, and low birth weight/prematurity were among the most consistently reported risk factors for ADHD (Thapar, Cooper, Eyre, & Langley, 2013). However, so far, true causality is not confirmed, as many of the reported associations may also arise from child or parent psychopathology, or stem from a third unknown variable. For example, maternal

smoking and alcohol use may exert their impact on ADHD outcome through more indirect pathways such as pleiotropic effects (i.e. one gene having an effect on multiple phenotypic outcomes); or ADHD symptoms may evoke family conflict instead of conflicts evoking ADHD; or mild early adversities may not be causally related to ADHD but may modify ADHD expression and further outcomes (Thapar et al., 2013). The interplay between environmental and genetic factors is suggested to be highly relevant: For example, familial genetic factors related to ADHD may increase the likelihood of exposure to certain environments with a certain adverse impact (Nigg, Nikolas, & Burt, 2010). Such patterns confirm the complex nature of the etiology of ADHD. As it is thought that the (interaction-) effects of genes and environment on ADHD outcomes are mediated through (dysfunctional) brain networks (the endophenotype model, Gottesman & Gould, 2003, see further for more detail), neurobiological and neurocognitive parameters are also one of the main targets of study in ADHD. This has led to a wealth of findings demonstrating differences in brain structure and/or functioning between children and adults with ADHD and those unaffected (see for a review for example Cortese et al., 2012; Durston, van Belle, & de Zeeuw, 2011; Frodl & Skokauskas, 2012; Hart, Radua, Mataix-Cols, & Rubia, 2012; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). Overall, findings show dysregulation of the prefrontal cortex and interconnected frontostriatal and frontocerebellar networks both in children and in adults (Cortese et al., 2012; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Durston et al., 2011). However, clearly there is large heterogeneity within ADHD as findings are not apparent in all individuals with ADHD (not being sensitive) or are also apparent in individuals without ADHD (not being specific), and findings are restricted due to methodological aspects (see for example van Ewijk et al., 2012). Also neurocognitive dysfunctions in ADHD have been studied intensively in the past decades and will be discussed in the next chapter. Summarizing, it appears that ADHD is the result of a complex interaction of genetic, neurobiological, neurocognitive (but see further), and environmental factors (Faraone et al., 2015; Faraone et al., 2005).

Insight into the Etiology of ADHD Using Neurocognitive Functioning

In this thesis, the term neurocognitive functioning refers to psychological processes that arise from neural processes in the brain, and relate to information processing abilities. Neurocognitive functioning is the overarching term for the quality of performance of specific neurocognitive functions (e.g., attention, memory, learning) that together may lead to overt behavior such as impulsive responses. By isolating specific neurocognitive functions using experimental paradigms we aim to get new insights into behavioral (dys)functioning, and its neurobiological underpinnings. As an illustration, studies have investigated attentional processes using a Continuous Performance Task (CPT, see for example Vaughn et al., 2011)), recorded ankle or chair

movements as a proxy for hyperactivity (see for example Sarver, Rapport, Kofler, Raiker, & Friedman, 2015), or measuring the ability to inhibit a prepotent response as an indicator of impulsive behavior using the Stop Task (see for an example Oosterlaan & Sergeant, 1996).

In ADHD, neurocognitive dysfunctions have been proposed at the heart of several theoretical models: in first instance, many theories proposed specific singular neurocognitive function(s) to underlie ADHD at the symptom level (e.g. Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant, 2000; Sonuga-Barke & Halperin, 2010; Sonuga-Barke, 2005). Experimental evidence in line with these theories suggests that in comparison to normally developing children, children with ADHD perform poorly at a group level in terms of neurocognitive functioning.

This perspective has been extended to the idea that there are three major domains of functioning, that are more or less neurobiologically independent from each other, which play a key role in ADHD: Impairments in cognitive control, reinforcement processing, and temporal processing (Castellanos & Tannock, 2002; Durston et al., 2011; Sonuga-Barke, Bitsakou, & Thompson, 2010; Wåhlstedt, Thorell, & Bohlin, 2009). These three domains can independently lead to ADHD, offering an explanation for neurocognitive and behavioral heterogeneity observed in ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). However, deficits in these three neurocognitive domains do not encompass all neurocognitive impairments observed in ADHD, as for example impairments in IQ, attention, basic information processing speed, perception, and emotion recognition may not be categorized in these three domains, but have also shown to be associated with ADHD (Faraone et al., 2015; Frazier, Demaree, & Youngstrom, 2004; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Nazari et al., 2010; Uekermann et al., 2010; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

A more recent approach is neurocognitive *profiling,* in which the specific pattern of performance (e.g. strengths and weakness) across tasks/domains within one individual is taken into account, a so-called person-based approach (Bergwerff, Luman, Weeda, & Oosterlaan, 2017; Fair, Bathula, Nikolas, & Nigg, 2012; Mostert et al., 2015; Rajendran, O'Neill, Marks, & Halperin, 2015; Rommelse, van der Meer, Hartman, & Buitelaar, 2016; van Hulst, de Zeeuw, & Durston, 2015). Such an approach acknowledges the complex interplay that may exist between neurocognitive functions. Different subgroups of children with ADHD have been identified based on distinct neurocognitive profiles (Bergwerff et al., 2017; Fair et al., 2012; Mostert et al., 2015; Rommelse et al., 2016; van Hulst et al., 2015), that are remarkably independent of the severity of ADHD symptoms. Intriguingly, similar profiles were observed in healthy control children (Fair et al., 2012; Mostert et al., 2015; van Hulst et al., 2015) and in unaffected siblings (Rommelse et al., 2016), highlighting that *differences in*

neurocognitive profiles per se are neither necessary nor sufficient to predict ADHD symptom levels. See Figure 1.2 for a visual summary of the three neurocognitive pathways to ADHD described so far, all acknowledging a causal role of neurocognitive functioning in ADHD.

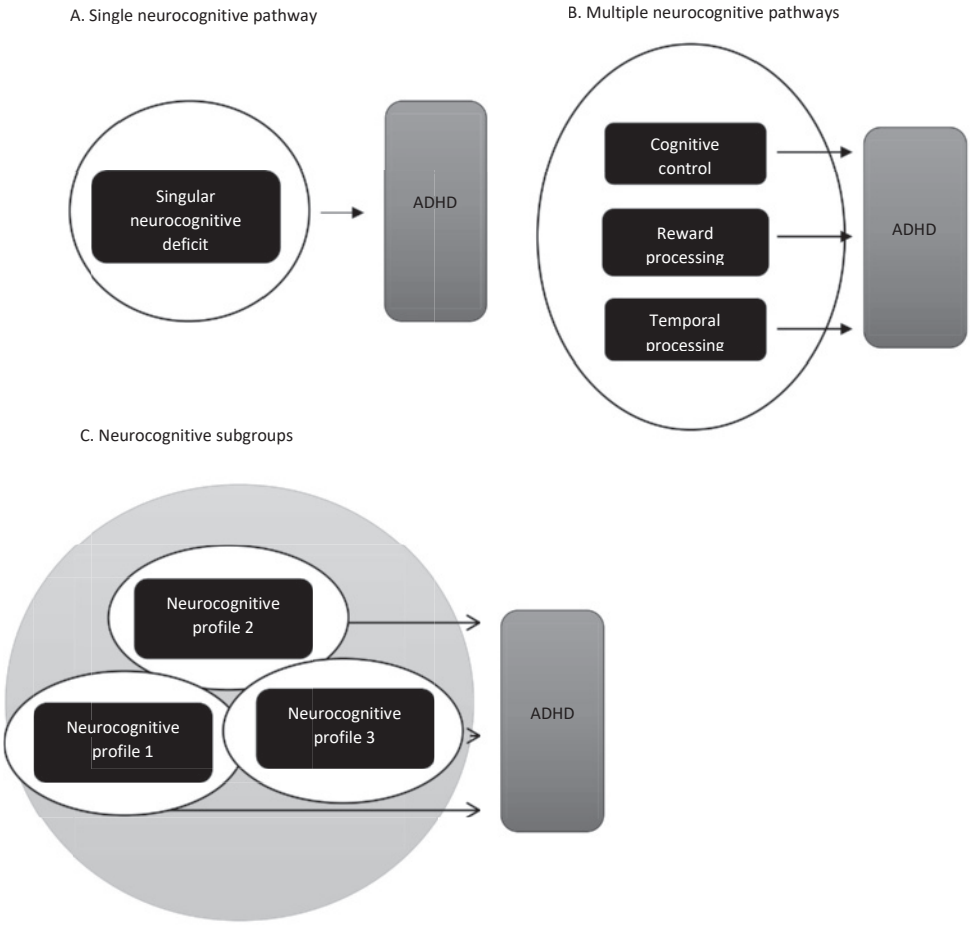

Figure 1.2. Visual summary of different neurocognitive pathways to ADHD.

A model that presents an holistic framework for ADHD and also acknowledges a causal role of neurocognition is the endophenotype model. This model connects genetics, neurobiology, neurocognitive functioning, environmental factors, and behavior and/or impairment. An endophenotype is a quantitative trait lying on the pathway between genes and phenotype, in which variation depends upon fewer genes than variation within the phenotype (Gottesman & Gould, 2003). The true mediating effect of neurocognitive functioning has not yet been established, but some evidence is available for heritability in which neurocognitive functions partly link to the same genes as the ADHD phenotype (Kuntsi et al., 2013). Traditionally, endophenotypes are used in the search for specific genes, but established endophenotypes may also be helpful in predicting the behavioral phenotype. Several studies for example have demonstrated that neurocognitive dysfunctions cluster within ADHD families and/or are heritable, indicating the potential usefulness as an endophenotype (Bidwell, Willcutt, Defries, & Pennington, 2007; Castellanos & Tannock, 2002; Kuntsi et al., 2006; Rommelse, Altink, Martin, et al., 2008a; Rommelse, Altink, Oosterlaan, et al., 2008b; Rommelse et al., 2007a; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007b; Uebel et al., 2010). According to the endophenotypes model, one would expect that better neurocognitive functioning (or larger improvement) relate to better behavioral outcomes and that worse neurocognitive functioning (or larger deterioration) would relate to worse behavioral outcomes.

In contrast to the models described above that stress that neurocognitive dysfunctions are part of a causative chain in ADHD, there is evidence to suggest that neurocognitive dysfunctions have no pertinent role in ADHD (Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014). In this study, only one out of nine neurocognitive functions (attentional set-shifting) predicted greater decrease in ADHD symptoms 10 years later. As a result, Coghill et al. (2014) have suggested that neurocognitive functions can at best be seen as some type of comorbid condition, related to the same underpinnings as ADHD symptoms, but not necessarily causally related to the disorder. Defined this way, neurocognitive functions may at best be seen as epiphenomena of ADHD. Possibly, the presence of co-occurring neurocognitive problems mark a more severe form of the disorder, as neurocognitive deficits and ADHD symptoms may independently contribute to impairment (Coghill et al., 2014).

Although the abovementioned models (e.g. multiple pathways, neurocognitive profiled subgroups, endophenotype or epiphenomenon) have specific predictions regarding the role of neurocognitive functioning in the etiology of ADHD, neither of the models has focused specifically on the role of neurocognitive functioning in the *course* of ADHD. One theory that explicitly has emphasized the relationship between the course of neurocognitive functions and the course of ADHD symptoms comes from Halperin & Schulz (2006). These authors differentiate between causal factors and recovery mechanisms, and hypothesize that ADHD is caused by a non-cortical (for example

basal ganglia, cerebellum: not involving *neo*cortical areas) neural dysfunction that is present early in life, remains relatively stable throughout the lifetime, and is not associated with remission of symptoms that often occurs in adolescence (Halperin & Schulz, 2006). The development of the prefrontal cortex (PFC) and associated circuits in early adolescence and in early adulthood may compensate for the behavioral deficits associated with the non-cortical neural dysfunction. This is reflected in the reduction of ADHD symptoms in late adolescence and early adulthood in a proportion of ADHD cases with (improved) strong cognitive control (Halperin & Schulz, 2006). In other words, neurocognitive deficits that remain present in both remitted and persistent cases, despite prefrontal cortex development, are suggested to have a core causal effect on the disorder. This model further predicts that children with the greatest developmental improvement in neurocognitive functions that require high levels of effort, such as cognitive control functions, are those who show remission from ADHD in adulthood. In Figure 1.3, these holistic etiological models are visualized.

In contrast to persisting core neurocognitive deficits in the model of Halperin & Schulz, the "maturational lag" hypothesis suggests that during development children with ADHD will remit from their ADHD symptoms and their impairments in neurocognitive functioning and will show catch-up with normative development (Berger, Slobodin, Aboud, Melamed, & Cassuto, 2013; Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005; Klein & Mannuzza, 1991; Shaw et al., 2007; Shaw et al., 2012). According to this theory, maturation of children with ADHD is not qualitatively different from controls, but 'just' delayed. This model however does not indicate through which etiological mechanisms this delay is apparent and whether neurocognitive functioning has a causal role therein.

Advances of the Current Study

Although knowledge on the disorder has increased exponentially, many questions remain. For example, it should be of great interest to know whether neurocognitive functions could serve as valuable predictors for the further course of ADHD, or whether their development is related to ADHD outcomes, to improve prognosis and understanding of the disorder. The main aim of the current thesis is to advance our knowledge on the role of neurocognitive functioning in the course of ADHD (symptom severity and overall functioning), using a longitudinal design. The current thesis adds to previous literature on the role of neurocognitive functioning in relation to the course of ADHD and outcome. Several of the methodological shortcomings of previous work were dealt with. First, available studies looking at the relationship between neurocognitive functioning and the course and outcome of ADHD have focused mainly on dichotomous outcomes (diagnosis yes/no), rather than on more sensitive continuous

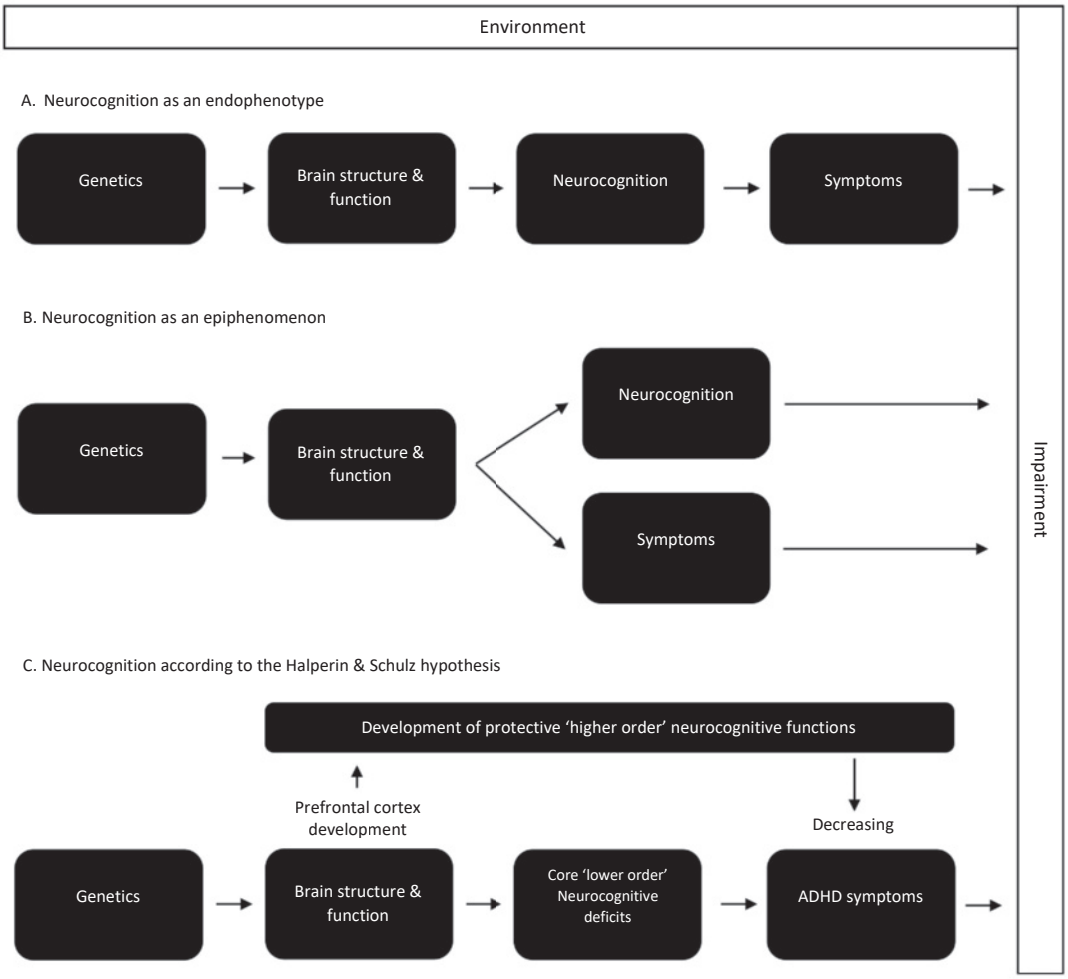

Figure 1.3. Visual summary of different models that included neurocognitive functioning in holistic pathways to ADHD. Figure 1.3A and 1.3B are inspired by Coghill et al., 2014. 'Environment' refers to bi-directional relationships with all levels in the several models. ADHD = Attention-Deficit/Hyperactivity Disorder.

measures of symptom severity that may provide a more fine-grained picture of the disorder (Lahey & Willcutt, 2010; Willcutt et al., 2012). Therefore, in addition to a thorough clinical diagnostic interview to establish a reliable ADHD diagnosis (see von Rhein et al., 2015 for further details), this thesis focused on continuous outcome measures (ADHD symptom severity, comorbid problems; **chapter 3-6**). Second, we took a continuous measure of overall functioning into account besides ADHD outcome (**chapters 3-6**). Thus far, most studies exclusively focused on ADHD core symptoms and did not assess accompanying levels of impairment. Outcome as measured in terms of the level of overall functioning (e.g. based on social, psychological, and academic functioning) may be clinically more relevant as it may relate more directly to the wellbeing of individuals. Third, in **all chapters**, we carefully investigated pharmacological treatment as a possible confounder. Currently, not many studies took pharmacological treatment into account, which may have a significant impact on ADHD outcomes (Faraone & Buitelaar, 2010). Fourth, with our large family based study we were able to improve on earlier literature with small sample sizes. Further, by including a sample with a large age range (5-19 years) and carefully investigating moderating effects of age, we aimed to take into account the possible effects of different age groups. This may be important, as significant developmental processes (neurobiological, psychological, neurocognitive) of an individual are ongoing from childhood through adolescence into adulthood, with a marked transition period in adolescence (Geier, 2013). However, so far, studies have investigated either a narrow age range, or did not specifically investigate effects of age in samples with a larger age range. Additionally, in **chapter 5 and 6** we investigated neurocognitive functions at two time points, with on average six years in between. So far, only a handful of studies included neurocognitive measurements at two time points when investigating the relationship between neurocognitive functioning and the course and outcome of ADHD. Also, we included a broad array of neurocognitive functions that we assumed important in ADHD, such as inhibition (**chapter 4**), verbal working memory, timing, variability, reaction time speed, motor control, IQ (**chapter 4-6**), and we also took into account an aggregated measure of neurocognitive functioning (**chapter 4**). This contrasts with earlier studies that mainly focused on one or two specific aspects of neurocognitive functioning.

An additional point of interest is that unaffected siblings are included in our study, an important group that may increase our understanding of the course of ADHD. Because siblings share one-half of their genes and several environmental risk factors, unaffected siblings are a different group compared with controls and it is assumed that they are at-risk for developing a full diagnosis. Also, developmental outcomes in this group 'at risk' can be studied independent of an ADHD diagnosis and treatment for ADHD at study entry. To our knowledge, neurocognitive functioning of unaffected siblings have been studied solely cross-sectionally, with mixed results showing that unaffected siblings performed worse than controls (Rommelse et al., 2007a), they

performed similar to their ADHD siblings (Bidwell et al., 2007; Pironti et al., 2014), they performed in between affected siblings and controls (Rommelse, Altink, Oosterlaan, et al., 2008b; Rommelse et al., 2008c), or they showed subtle or no deficits in contrast to their affected siblings (Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005; Fliers et al., 2010; Rommelse et al., 2008c; Rommelse et al., 2007b; Seidman, Biederman, Monuteaux, Weber, & Faraone, 2000). In **chapter 5 & 6**, we included unaffected siblings to achieve a sample that displays a continuum of ADHD symptoms, and with the abovementioned characteristics, unaffected siblings also may shed new light on pathophysiological mechanisms in ADHD.

Study Design

Participants in the studies that we describe in this thesis originally came from the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study. Between 2003 and 2006, the IMAGE study recruited families with at least one child with clinically diagnosed ADHD combined subtype (ADHD/C) and at least one additional sibling regardless of possible ADHD status. In addition, control families with at least one child, with no formal or suspected ADHD diagnosis in any of the first-degree family members were included. Inclusion criteria for study entry at baseline were an age of 5-19 years, Caucasian descent, IQ $\geq$ 70, no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, and known genetic disorders (Müller et al., 2011a, 2011b). Extensive information was collected from both children as well as their parents; from a clinical diagnostic interview for ADHD and comorbid disorders, behavioral questionnaires, neurocognitive assessment, to genetic phenotyping.

On average six years later, between 2009-2012, we re-invited all participants for a comprehensive follow-up assessment as part of the NeuroIMAGE study. Again, families were invited for an entire testing day. Similar as well as new phenotypic measures compared to those collected within the IMAGE study were obtained. In addition, structural and functional neurobiological measures (via magnetic resonance imaging, MRI) were collected in children in the NeuroIMAGE study. Testing took place at the Vrije Universiteit Amsterdam, or at the Donders Institute in Nijmegen. See for a complete description von Rhein et al. (2015). In this thesis, behavioral as well as neurocognitive data from the baseline and follow-up measurement were used.

Aims and Outline of this Thesis

As described above, the main aim of the current thesis is to advance our knowledge on the role of neurocognitive functioning in the course of ADHD (symptom severity and overall functioning), using a longitudinal design. Children with ADHD/C are the main focus in this thesis, but we additionally investigated a full spectrum of the ADHD continuum by including their unaffected siblings and controls (**chapter 5 & 6**). This thesis has two specific sub aims. The first is to chart the course of ADHD (symptom change and persistence rates) and of neurocognitive functioning. The second is to predict ADHD outcomes (symptom severity, overall functioning, and comorbid problems). More specifically, ADHD outcomes will be predicted from: (1) baseline behavioral characteristics, (2) baseline neurocognitive functioning, and (3) longitudinal information (baseline and follow-up) on neurocognitive functioning (see Figure 1.1). Ultimately, findings from this dissertation could contribute to more accurate prognostic tools, thereby providing input on psychoeducation to individuals with ADHD and their families, and guide treatment planning.

First, in **Chapter 2,** a systematic review of the literature is provided on the predictive value of neurocognitive functioning for future ADHD (status of persistence/remittance and symptoms). Results will be discussed in the light of the Halperin & Schulz model (2006), and future directions are provided. In **Chapter 3**, the six-year outcome of participants with ADHD/C from the NeuroIMAGE cohort is investigated. ADHD persistence rates, comorbidity rates, symptom severity and overall functioning are used as outcome measures. In addition, baseline predictors of ADHD outcomes (ADHD symptom severity and overall functioning) are assessed, including demographics, ADHD familiality, ADHD severity, comorbidities and pharmacological treatment. The impact of continued pharmacological treatment until follow-up is investigated within the prediction models of ADHD symptom severity and overall functioning. **Chapter 4-6** include a broad array of neurocognitive measures. **Chapter 4** specifically focuses on baseline neurocognitive predictors of ADHD outcomes in participants with ADHD/C. In **Chapter 5**, the full ADHD spectrum is studied by including unaffected siblings and controls next to ADHD/C affected siblings. Subsequently, we map the course of neurocognitive functioning onto dimensional ADHD outcomes (symptoms and overall functioning) at follow-up. **Chapter 6** also uses longitudinal information on a broad array of neurocognitive functions, aiming to identify solid distinct longitudinally informed neurocognitive subgroups, and to examine how these empirically based neurocognitive subgroups mapped onto the ADHD phenotype. Finally, **chapter 7** summarizes and discusses key findings, and provides and overview of the limitations of the studies and recommendations for future studies.

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2

CHAPTER 2

Does Neurocognitive Functioning Predict Future or Persistence of ADHD? A Systematic Review

van Lieshout, M., Luman, M., Buitelaar, J., Rommelse, N.N.J., & Oosterlaan, J. (2013). Does neurocognitive functioning predict future or persistence of ADHD? A systematic review. *Clinical Psychology Review, 33*(4), 539-560.

Abstract

Background. Many children with ADHD remain symptomatic in (young) adulthood. It is important to understand what characterizes this persistent ADHD group. Since ADHD has been associated with neurocognitive dysfunctioning on a variety of neurocognitive domains, and many of these domains are influenced by the same risk genes that influence ADHD, neurocognitive functions are a potential predictor for ADHD persistence.

Methods. We carried out a systematic literature review on the predictive value of neurocognitive functioning for future ADHD.

Results. Based on eighteen studies there was no evidence that either automatically controlled (requiring little mental effort; lower level), or more consciously controlled (requiring high levels of mental effort; higher level) neurocognitive functions differentiated ADHD persistence from remittance. In general, both persisters and remitters showed weaker performance than typically developing controls, although the effect was smaller for remitters. Neurocognitive functions measured in childhood predicted ADHD a few years later, regardless of the type of neurocognitive function.

Conclusion. Our findings do not support the model of Halperin & Schulz (2006), which suggests a maturation of more consciously controlled neurocognitive functions in ADHD remitters.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common developmental disorder, affecting around 5% of children and adolescents (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and 2.5% of adults (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). The decrease in prevalence from ADHD in childhood to adulthood implies an age-related symptom decline. A meta-analysis on retention of ADHD over time showed that, starting at age nine, every five years the rate of ADHD declines by 50% (Hill & Schoener, 1996). This is particularly true for symptoms of hyperactivity/impulsivity, but much less so for symptoms of inattention. Symptoms of inattention appear relatively stable with advancing age (Hart, Lahey, Loeber, Applegate, & Frick, 1995). When applying strict versus loose definitions of persistence (i.e. meeting full diagnostic criteria for ADHD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association [APA, 1994]) versus meeting DSM-IV ADHD in partial remission criteria), 15% versus 65% of children remain symptomatic at age 25 follow-up (Faraone, Biederman, & Mick, 2006). A more recent study showed that even 70% of children with a childhood diagnosis of ADHD continued to meet full ADHD DSM-IV criteria in adolescence (Langley et al., 2010). These data thus show that large proportions of children have persistent and impairing symptoms of ADHD in young adulthood.

For early detection and intervention of persistent ADHD, it is important to understand what determines whether a child remains symptomatic or not. In other words, can we identify predictive factors for the course of ADHD symptoms and diagnosis? These factors may include genetic risk, structural and functional brain characteristics, neurocognitive functioning, behavior, and environmental factors. Currently, our knowledge on predictive factors is foremost based on behavioral and environmental variables. A large well-described cohort of participants with persistent ADHD measured in adulthood, showed that a family history of ADHD, psychosocial adversity, co-morbidity, and the number and severity of childhood symptoms, predicted persistence of ADHD (Biederman et al., 1996; Biederman, Petty, Clarke, Lomedico, & Faraone, 2011). These findings have been supported by an international World Health Organization (WHO) study (Lara et al., 2009). A large-scale population-based study on adult ADHD, however, found support only for severity of childhood ADHD and childhood treatment as predictors for persistent ADHD (Kessler et al., 2005). Up to now, the causal mechanisms between these behavioral predictors and the persistence of ADHD remain unclear.

Assessing the predictive value of neurocognitive functioning in relation to the persistence of ADHD is potentially of great value, because neurocognitive functioning is robustly associated with ADHD. Several models of neurocognitive impairments in

ADHD have been proposed (e.g. Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant, 2000; Sonuga-Barke, 2005), supported by studies showing that children with ADHD generally performed poorly in terms of neurocognitive functioning compared to normally developing children. Three major domains of neurocognitive impairment are found to play a key role in ADHD and appear at least to some degree neurobiologically independent from each other: impairments in cognitive control, reinforcement processing, and temporal processing (Castellanos & Tannock, 2002; Durston, van Belle, & de Zeeuw, 2011; Sonuga-Barke, Bitsakou, & Thompson, 2010; Wåhlstedt, Thorell, & Bohlin, 2009). However, deficits in these three neurocognitive domains do not encompass all neurocognitive impairments observed in ADHD, as for example impairments in IQ, attention, basic information processing speed, perception, and emotion recognition may not be categorized in these three domains, but have also shown to be associated with ADHD (Frazier, Demaree, & Youngstrom, 2004; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Nazari et al., 2010; Uekermann et al., 2010; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

The relation between neurocognitive functioning and ADHD is also demonstrated in studies showing that neurocognitive dysfunctions are potentially useful as endophenotypes (Castellanos & Tannock, 2002; Rommelse, Altink, Martin et al., 2008; Rommelse, Altink, Oosterlaan et al., 2008; Rommelse, Altink et al., 2007; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007; Uebel et al., 2010). An endophenotype is a quantitative trait lying on the pathway between genes and phenotype, in which variation depends upon fewer genes than variation within the phenotype (Gottesman & Gould, 2003). The true mediating effect of these neurocognitive domains is not yet established, but at least for most domains sufficient evidence is available for heritability in which the domains partly link to the same genes as the ADHD phenotype. Traditionally endophenotypes are used in the search for -and unraveling of- the working mechanisms of specific genes, but established endophenotypes may also be helpful in predicting the behavioral phenotype. The abovementioned characteristics suggest that neurocognitive functions can be valuable predictors for persistence of ADHD symptoms or diagnosis.

Which of the associated neurocognitive deficits is most strongly related to persistence of ADHD is largely unknown. It has been hypothesized that ADHD is caused by a non-cortical (for example basal ganglia, cerebellum: not involving *neo*cortical areas) neural dysfunction that is present early in life, remains relatively stable throughout the lifetime, and is not associated with remission of symptoms that often occurs in adolescence (Halperin & Schulz, 2006). The development of the prefrontal cortex (PFC) and associated circuits in early adolescence and in early adulthood compensates for the behavioural deficits associated with the non-cortical neural dysfunction. This is reflected in the development of improved cognitive control and the reduction of ADHD symptoms in late adolescence and early adulthood in a proportion of ADHD cases

(Halperin & Schulz, 2006). In other words, neurocognitive deficits that remain present in both remitted and persistent cases, despite prefrontal cortex development, are suggested to have a core causal effect on the disorder. Neurocognitive deficits that normalize concurrently with behavioral symptom recovery are seen as epiphenomena (Carr, Nigg, & Henderson, 2006). This model predicts that children with the greatest developmental improvement in neurocognitive functions that require high levels of effort, such as cognitive control functions, are those who show remission from ADHD in adulthood.

The aim of this review was to investigate the predictive value of neurocognitive functioning for ADHD persistence, ADHD remittance and control status, and for future ADHD diagnosis and symptoms. We hypothesized that there are differences in predictive value between domains of neurocognitive functions, as indicated by the model of Halperin & Schulz (2006). This model indicates that (changes in) neurocognitive functions requiring a high level of effort (from here on referred to as 'higher level' neurocognitive functions) are predictive for ADHD persistence and ADHD remittance, as ADHD remitters are predicted to show normalization of these functions. This is shown at the left side of Figure 2.1. In contrast, less consciously controlled, more automatic neurocognitive functions (from here on referred to as 'lower level' neurocognitive functions) are poorly developed in both ADHD persisters and ADHD remitters, and thus have no predictive value for differentiating between the two groups, which is shown at the right side of Figure 2.1. Studies on the predictive value of neurocognitive functions would deepen our understanding of the mechanisms involved in the persisting course of ADHD. At a more practical level, it would provide us a tool to identify children with ADHD who are at risk for future ADHD or for a persistent course into adulthood.

Methods

The computerized databases PubMed, Web of Knowledge and PsycInfo were used to retrieve relevant studies. The following search terms and equivalents generated by the search engines were used to search in both title and text: follow-up, longitudinal, ADHD, attention-deficit/hyperactivity disorder, attention deficit disorder with hyperactivity, attention deficit disorder, hyperkin*, AD/HD, ADDH, neuropsycho*, neurocognitive, cognitive. The reference lists of retrieved articles were used to locate other relevant studies.

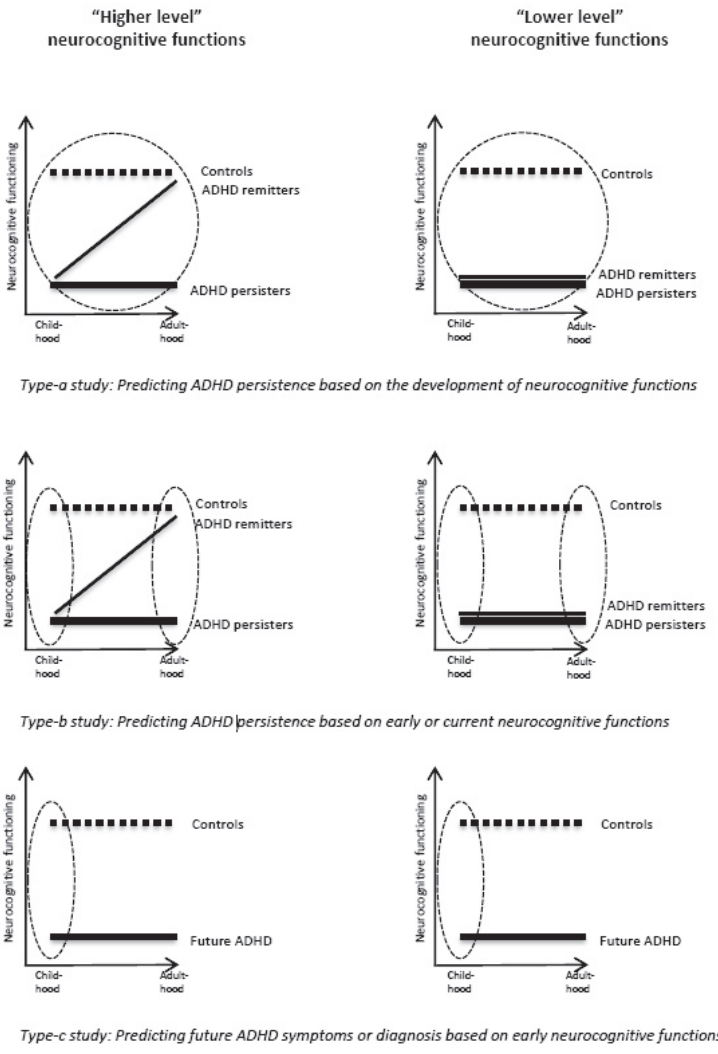

Figure 2.1. Schematic of the expected differences between ADHD persisters, ADHD remitters, and controls in terms of neurocognitive functions, according to study design (see main text for explanation of study designs). Neurocognitive functions requiring a high level of effort are referred to as 'higher level' neurocognitive functions, and less consciously controlled, more automatic neurocognitive functions are referred to as 'lower level' neurocognitive functions. Hypotheses are based on the model postulated by Halperin & Schulz (2006). The dotted circle(s) indicate the time of measurement of neurocognitive functions that were used as a predictor for ADHD persistence or future ADHD. Two dotted circles in one graph indicate that the different times of neurocognitive measurement were studied separately for its predictive value.

Three different study designs were of interest: (a) the development of childhood neurocognitive functioning (multiple assessments of neurocognitive functioning over time) differentiating ADHD persistence, ADHD remittance, and control status, or predicting ADHD symptom development, (b) early neurocognitive functioning or current neurocognitive functioning (single assessment of neurocognitive functioning), differentiating ADHD persistence, ADHD remittance, and control status, or predicting ADHD symptom development, and (c) early neurocognitive functioning predicting *future* ADHD diagnosis and/or symptoms (see also Figure 2.1). These type-c studies thus will not report on the (symptom) *persistence* of ADHD. Type-b studies also include studies investigating neurocognitive functions that are measured concurrently with the assessment of ADHD persistence and ADHD remittance, to get insight into which neurocognitive deficits may ameliorate in the ADHD remittance group. Regardless of premorbid neurocognitive performance of ADHD persisters and remitters, it is very unlikely that a neurocognitive function that is currently still affected, is related to the remission of ADHD behavior. Current neurocognitive functioning thus is of additional relevance in characterizing ADHD persistence and remittance.

Studies were included that (1) used a longitudinal design in which neurocognitive measures were obtained in relation to ADHD persistence/remittance or ADHD symptom development, or in relation to future ADHD diagnosis or symptoms (2) used a follow-up period of at least six months between sequential assessments to avoid overlap between symptom reports (since the DSM requires ADHD symptoms to exist for at least six months), (3) used DSM-III-Revised (DSM-III-R) or DSM-IV/DSM-IV-Text Revision (DSM-IV-TR) criteria to establish concurrent ADHD diagnosis or symptoms, (4) compared ADHD persisters with ADHD remitters, compared ADHD remitters with controls, or compared ADHD persisters with controls when using group comparisons (for type-a and type-b studies); used a typically developing control group when using group comparisons (for type c-studies); (5) were not confounded by effects of treatment trials, and (6) were published in an English language peer-reviewed journal.

From the 827 studies that were retrieved through the search, fourteen studies met inclusion criteria. Additionally, we found four studies using the reference lists of retrieved studies, resulting in a total of eighteen studies meeting inclusion criteria, covering thirteen independent study samples. As a result of our focus on studies using DSM-III-R and DSM-IV(-TR) criteria at study entry, included studies were published between 1990 and 2011. Some studies were excluded because these studies reported on the same data already covered by a more comprehensive study report. Specifically, the studies of Biederman et al. (2011) and Von Stauffenberg and Campbell (2007) were not included in the review because results reported in these studies were covered in Biederman et al. (1996), Biederman, Petty, Ball et al. (2009), and Campbell and Von Stauffenberg (2009), respectively. If multiple studies reported on different aspects of

neurocognitive functioning in the same sample, these studies were all included (Milwaukee study: Barkley & Fischer, 2011; Fischer, Barkley, Smallish, & Fletcher, 2005 - New York study: Bédard, Newcorn, Trampush, & Halperin, 2010; Halperin, Trampush, Miller, Marks, & Newcorn, 2008 - Boston study: Biederman et al., 1996, Biederman, Petty, Ball et al., 2009 - Uppsala study: Brocki, Eninger, Thorell, & Bohlin, 2010; Brocki, Nyberg, Thorell, & Bohlin, 2007 - Maastricht study: Kalff et al., 2005; Kalff et al., 2002).

We describe results for several neurocognitive domains reported on in the literature, grouping results in terms of type-a, -b, and -c studies. First, we show the results for the three main domains of neurocognitive functioning: cognitive control, reward processing and temporal processing. Thereafter, we describe findings for other domains of neurocognitive functioning, including intelligence, attention, visual information processing, and basic information processing speed. In the interest of readability, four points are of importance. First, this review describes the prediction of ADHD persistence, rather than remittance, keeping in mind that cases that do not persist are those cases that show remittance. Also, if no results are reported for a particular study design, this indicates that no literature was retrieved for that particular study design. Third, for type-a and type-b studies, we describe how many studies investigated the design, and then report how many studies showed differences between (two) groups. This implicates that, if not otherwise stated, the studies that are not described, did not find differences between the (two) groups. When none of the studies showed differences between (two) groups, we report which studies did not find differences between the groups. Last, although included studies used several terms and definitions to describe ADHD persistence (see Biederman, Mick, & Faraone [2000] for a discussion), in our main text we use the terms (ADHD) persisters and (ADHD) remitters. Table 2.1 includes nuanced definitions.

It should be noted that many neurocognitive tasks tap into multiple domains of functioning and that for some task measures consensus lacks which primary function is assessed. We have used the most widely accepted measurement potential of a task measure to decide which domain was assessed by that particular task. We report results without adjustment for IQ, since IQ can remove ADHD related variance when used as covariate (Dennis et al., 2009). However, for one study that did not report results without adjustment for IQ, results were reported with IQ adjustment (Kalff et al., 2002).

Results

For each of the studies included in this review, Table 2.1 displays the study design, follow-up period, number of participants and selection procedure, age of the participants, neurocognitive measures, behavioral (criterion) measures, and results. For each neurocognitive domain, we describe the relevant studies ordered by the design employed (type-a, -b, or -c studies) as reported in the first column of Table 2.1. Thus, for each domain, first, we report on type-a studies (Biederman, Petty, Ball, et al., 2009; Fischer et al., 2005; Vaughn et al., 2011). Second, we report on type-b studies, starting with studies on the predictive value of early neurocognitive functions (Bédard et al., 2010; Biederman et al., 1996; Biederman, Petty, Ball et al., 2009; Hart et al., 1995; Langley et al., 2010; Mick et al., 2011), followed by studies on concurrently measured neurocognitive functions (Barkley & Fischer, 2011; Bédard et al., 2010; Biederman, Petty, Ball et al., 2009; Fischer et al., 2005; Halperin et al., 2008; Mick et al., 2011). Finally, we report on type-c studies (Berlin, Bohlin, & Rydell, 2003; Brocki et al., 2010; Brocki et al., 2007; Campbell & von Stauffenberg, 2009; Kalff et al., 2005; Kalff et al., 2002; Langley et al., 2010; Marakovitz & Campbell, 1998; Wåhlstedt, Thorell, & Bohlin, 2008). In the study of Halperin and colleagues (2008), ADHD persisters and remitters were not compared to each other because of limited group numbers. Results reported from that study (in the neurocognitive domains of inhibition, interference control, working memory, aggregated executive functioning (EF), temporal processing, alerting attention, intelligence, and basic information processing speed) thus only contain comparisons between persisters and controls, and between remitters and controls, respectively.

Cognitive Control

Cognitive control is the ability to flexibly adjust behavior to changing environmental demands (Nigg & Casey, 2005). Inhibition, working memory, interference control, set-shifting and planning are functions covered by this overarching term. Studies investigating these domains are discussed below. From a neurobiological perspective, cognitive control is thought to rely on the dorsal frontostriatal circuit, involving prefrontal areas, the striatum, and thalamus (Durston et al., 2011). Mainly the prefrontal areas do not mature until late adolescence (Luna, Padmanabhan, & O'Hearn, 2010), making cognitive control one of the latest maturing neurocognitive domains described in this review (Casey, Jones, & Somerville, 2011). Frontal dysfunction and cognitive control deficits are present in both children (Martinussen et al., 2005; Willcutt et al., 2005) and adults with ADHD (Bálint et al., 2009; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011; Desjardins, Scherzer, Braun, Godbout, & Poissant, 2010; Kobel et al., 2010), suggesting that cognitive control deficits remain present in at least some cases

Table 2.1. Prospective studies into the predictive value of neurocognitive measures for future (persistence of) ADHD diagnosis or symptoms

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
1. Barkley & Fischer, 2011				
Type-b study[c] $N_1 \rightarrow B_{0\text{-}1}$	T_0 Baseline	158 hyperactive children. Clinical sample. 81 controls. Community sample.	n.a. (4 – 12 year)	No measurements
	T_1 +/- 20 year follow-up	23 hyperactive children and 6 control children dropped out.	ADHD full/partial persisters: 26.8 (*SD* = 1.4) ADHD full remitters: 27.2 (*SD* = 1.4) Controls 27.0 (*SD* = 0.9)	- WAIS-III Vocabulary (verbal IQ measured by a scaled score) - WAIS-III Block Design (nonverbal IQ measured by a scaled score) - Stroop Color Word Test (interference control measured by the interference score) - WAIS-III Digit Span (verbal working memory measured by a combined forwards and backwards score) - KHM Test (nonverbal working memory measured by number correct and by longest sequence completed) - Simon game (nonverbal working memory measured by longest correctly reproduced sequence) - Five-Points Test of Design Fluency (nonverbal fluency measured by number of unique designs) - Tower of London Test (planning measured by total score, number correct to first trial and time to first move)
2. Vaughn et al., 2011				
Type-a study $N_{1\text{-}2} \rightarrow B_{1\text{-}2}$	T_0 Baseline	579 children with ADHD. Clinical sample.	n.a. (7.0 – 9.9 year)	No measurements
	$T_1$2 year follow-up	204 children with incomplete data dropped out leaving 375 children with ADHD (80.3% boys). 220 controls (81.0% boys) were additionally selected from a population sample chosen to be proportional to	ADHD: 10.4 year (*SD* = 0.85) Controls: 10.5 year (*SD* = 1.08)	- CPT (inhibition measured by commission errors - stability of temporal processing measured by *SD* of RT - alerting attention measured by mean RT and omission errors)

Behavioral measures (criterion)[b]	Results
P questionnaires combined with additional information, highly likely fulfilling ADHD DSM-III-R criteria.	
C DSM-IV structured interview: • 55 ADHD full/partial persisters • 80 ADHD full remitters • 75 controls	• Full/partial persisters = full remitters < controls: T_1 scaled scores (WAIS-III Vocabulary and Block Design). T_1 combined forwards and backwards score (WAIS-III Digit Span). T_1 number correct and longest sequence completed (KHM Test). T_1 longest correctly reproduced sequence (Simon game). T_1 number of unique designs (Five-Points Test). • Full/partial persisters > full remitters = controls: T_1 interference score (Stroop Color Word Test). • Other predictor effects were not significant.
P and T ratings DSM-IV criteria for: • ADHD/I symptoms • ADHD hyperactivity symptoms • ADHD impulsivity symptoms	

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
		ADHD sample in terms of relevant characteristics).		
	T_2 3 year follow-up	413 ADHD 212 controls[d]	ADHD: 11.5 year (*SD* = 1.18) Controls: 11.6 year (*SD* = 0.92)	- CPT (same measures as baseline) → change N_2-N_1 was used as predictor.
3. Mick, Byrne, Fried, Monuteaux, Faraone, & Biederman, 2011				
Type-b study N_0 → $B_{0\text{-}1}$ N_1 → $B_{0\text{-}1}$	T_0 Baseline	140 girls with ADHD. Clinical sample. 122 girls controls. Population sample.	(6 - 17 year)	- WISC-III/WAIS-III Vocabulary & Block Design (IQ measured by an aggregated measure of standard scores (TIQ) - ROCF, auditory CPT, WCST, CVLT child / CVLT-II, Stroop Color Word Task, WISC-III / WAIS-III DS, DSy/Co, SS (binary indicator of 'executive functioning deficit' defined by two or more deviating scores on subtests) - WISC-III/WAIS-III Arithmetic & Digit Symbol Coding (FFD measured by an aggregated measure of standard scores)
	T_1 5 year follow-up	17 children with ADHD and 16 controls with incomplete data dropped out.	ADHD 16.4 years (*SD* = 3.8) Controls 16.9 years (*SD* = 3.0)	- Same as baseline.
4. Bédard, Newcorn, Trampush, & Halperin, 2010				
Type-b study N_0 → $B_{0\text{-}1}$ N_1 → $B_{0\text{-}1}$	T_0 Baseline	169 children with ADHD. Clinical sample.	(7 – 11 year)	- WISC-III (IQ measured by an aggregated measure of standard scores (FSIQ))
	T_1 9.3 year follow-up (*SD* = 1.69)	80 children dropped out leaving 89 children originally diagnosed with ADHD for follow-up. 85 controls were additionally selected from a population sample chosen to be proportional to ADHD sample in terms of relevant characteristics.	(16-21 year)	- WAIS-III (IQ measured by an aggregated measure of standard scores (FSIQ)) - SRCT condition 1-3 (interference control measured by RT and accuracy - stability of temporal processing measured by *SD* of RT) -SRCT condition 4 & 5 (interference control measured by RT and accuracy - stability of temporal processing measured by *SD* of RT)

Behavioral measures (criterion)[b]	Results
P and T ratings DSM-IV criteria for: • ADHD/I symptoms • ADHD hyperactivity symptoms • ADHD impulsivity symptoms → symptom change B_2-B_1 was used as outcome.	After adjustment for medication effects: • No predictor effects were significant.
P DSM-III-R structured interview (ADHD) and P DSM-III-R telephone questionnaire (controls).	
P & C DSM-IV (semi-) structured interview: • 79 ADHD full/partial persisters • 44 ADHD full remitters • 106 Controls	After adjustment for age effects at follow-up: • Full/partial persisters = full remitters < controls T_0 and T_1 TIQ and FFD. • Full/partial persisters = full remitters > controls T_0 and T_1 executive functioning deficits. • Other predictor effects were not significant.
P & T DSM-III-R interview/questionnaires[e].	
P & C DSM-IV semi-structured interview • 38 ADHD full persisters • 29 ADHD full remitters • (85 controls, only when SRCT was analyzed)	• Full persisters < controls T_1 RT and accuracy (SRCT condition 1 & 3 / 4 & 5). • Full persisters > controls T_1 *SD* of RT (SRCT condition 1 & 3 / 4 & 5). • Full remitters < controls T_1 RT and accuracy (SRCT condition 1 & 3) and RT (SRCT condition 4 & 5). • No other predictor effects were significant.

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
		(88 % boys in complete sample)		
5. Brocki, Eninger, Thorell, & Bohlin, 2010				
Type-c study $N_0 \rightarrow B_2$ $N_1 \rightarrow B_2$	T_0 Baseline	72 children (60 boys). 1/3 from clinical sample and 2/3 from random population. Sample chosen to be proportional to clinical sample in terms of gender and age.	5.4 year (*SD* = 0.69)	- Go/No-Go Task (inhibition measured by commission errors) - Auditory Attention subtest NEPSY (orienting attention measured by total score)
	T_1 14 month follow-up (*SD* = 0.13)	4 children dropped out leaving 68 children for follow-up.	6.3 year (*SD* = 0.68)	- Go/No-Go Task (simple inhibition measured by commission errors) - Stroop-like task (interference control measured by number of correct responses) - Children's Size-Ordering Task (verbal working memory measured by total number of pairs ordered correctly)
	T_2 26 month follow-up (*SD* = 0.28)	7 children dropped out leaving 65 children for follow-up.	7.5 year (*SD* = 0.47)	No measurements
6. Langley et al., 2010				
Type-a study $N_0 \rightarrow B_{0\text{-}1}$ Type-c study $N_0 \rightarrow B_1$	T_0 Baseline	157 children with ADHD. Clinical sample.	9.4 year (6-13 year, *SD* = 1.7)	- WISC-III (IQ measured by an aggregated measure of standard scores (FSIQ))
	T_1 5 year follow-up	31 children with incomplete data dropped out leaving 126 children for follow-up (118 boys).	14.5 year (12-18 year, *SD* = 1.7)	No measurements

Behavioral measures (criterion)[b]	Results
P and T ratings of DSM-IV ADHD criteria for: • ADHD/I symptoms • ADHD/H symptoms	After adjustment for age effects: • Positively predicting ADHD/H and ADHD/I symptoms: T_0 commission errors (Go/No-Go task) (r = .37 and r = .30). • Negatively predicting ADHD/H symptoms: T_1 number of correct responses (Stroop-like task) (r = -.47). • Negatively predicting ADHD/I symptoms: T_0 total score (Auditory Attention subtest) (r = -.32). T_1 total number of pairs ordered correctly (Children's Size-Ordering Task) (r = -.28). T_1 number of correct responses (Stroop-like task) (r = -.68). • Other predictor effects were not significant.
P & T DSM-IV semi-structured interview.	
P & T semi-structured interview for DSM-IV: • 88 ADHD • 33 no ADHD → Both ADHD diagnosis and a symptom change score were used as outcome.	After adjustment for medication and age effects: • No predictor effects were significant.

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
7. Biederman, Petty, Ball, Fried, Doyle, Cohen, Henderson, & Faraone, 2009				
Type-a study $N_{0\text{-}1\text{-}2} \rightarrow B_{0\text{-}2}$ Type-b study $N_0 \rightarrow B_{0\text{-}1}$ $N_1 \rightarrow B_{0\text{-}1}$ $N_2 \rightarrow B_{0\text{-}1}$	T_0 Baseline	260 boys. clinical and random (controls) population sample.	(6 - 17 year)	- WISC-R/WAIS-R Vocabulary, Block Design (Verbal IQ measured by a scaled score on the Vocabulary subtest - Performance IQ measured by a scaled score on the Block Design subtest - IQ measured by an aggregated measure of standard scores (TIQ)) - WISC-R/WAIS-R Digit Span (verbal working memory measured by a scaled score on this subtest (not further explained)) - WSC-R/WAIS-R Digit Symbol (basic processing speed measured by a scaled score on this subtest (not further explained)
	T_1 4 year follow-up	33 children with incomplete data dropped out leaving 237 children for follow-up.	14.33 years	- Same as T_0 and in addition: - WISC-R/WAIS-R Arithmetic, Digit Span, Digit Symbol, ROCF, computerized WCST , Stroop Color Word Test (neuropsychological aggregate measured by a composite z-score)
	T_2 10 year follow-up		ADHD full/partial persisters 20.5 years (*SD* = 3.2) ADHD full remitters 22.4 years (*SD* = 3.1) Controls 22.0 years (*SD* = 4.0)	- Same as T_1 but WISC-R and WAIS-R were replaced by WISC-III and WAIS-III
8. Campbell & Von Stauffenberg, 2009				
Type-c study $N_1 \rightarrow B_4$ $N_2 \rightarrow B_4$ $N_3 \rightarrow B_4$	T_0 Baseline	1,364 children. Random population sample.	1 m (n.a.)	No measurements
	T_1 35 months follow-up	Not reported.	3 year (n.a.)	- Forbidden Toy Situation (reward delay aversion measured by latency to first active engagement)
	T_2 53 months follow-up	Not reported.	4.5 year (n.a.)	- Delay of Gratification Task (reward delay aversion measured by waiting time)

Behavioral measures (criterion)[b]	Results
P and C structured DSM-III-R interviews with supplemented questions according to DSM-IV criteria: • 140 boys with ADHD • 120 controls	
Assignment to one of following groups based on P and C structured DSM-IV interview: • 57 ADHD full/partial persisters • 33 ADHD full remitters • 72 controls	After adjustment for ascertainment source and age effects: • Full/partial persisters > full remitters = controls $T_{0\text{-}1\text{-}2}$ decrease over time on TIQ (WISC/WAIS Vocabulary and Block Design). • Full/partial persisters = full remitters > controls $T_{0\text{-}1\text{-}2}$ decrease over time on Block Design scaled score (WISC/WAIS). • Full/partial persisters = full remitters < controls T_0, T_1 and T_2 scores of all other neurocognitive tasks. • Other predictor effects were not significant.

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
				- CPT (inhibition and alerting attention measured by commission errors and omission errors, respectively)
	T_3 1st grade follow-up	Not reported .	Not reported.	- Tower of Hanoi (planning measured by total planning efficiency score) - CPT (different version as compared to 53 months) (inhibition and alerting attention measured by commission errors and omission errors, respectively)
	T_4 3rd grade follow-up	281 children with incomplete data dropped out leaving 1,082 children for follow-up.	Not reported.	No measurements
9. Halperin, Trampush, Miller, Marks, & Newcorn, 2008				
Type-b study $N_1 \rightarrow B_{0\text{-}1}$	T_0 Baseline	169 children with ADHD. Clinical sample.	(7 – 11 year)	No measurements
	T_1 9.3 year follow-up (*SD* = 1.65)	80 children dropped out leaving 89 children originally diagnosed with ADHD for follow-up. 85 controls were additionally selected from a population sample chosen to be proportional to ADHD sample in terms of relevant characteristics.	(16-21 year)	- WAIS-III Vocabulary, Similarities and Information (verbal comprehension measured by an aggregated measure of standard scores (VCI)) - WAIS-III Picture Completion, Block Design, Matrix reasoning (perceptual organization measured by an aggregated measure of standard scores (POI))

Behavioral measures (criterion)[b]	Results
Membership of one of three ADHD groups. Subsample derived on the basis of T & P DSM-IV questionnaires: • 57 ADHD/C (70% boys) • 80 ADHD/I (64% boys) • 790 Controls (44% boys)	After adjustment for maternal education and gender effects: • ADHD/C < ADHD/I < controls: T_2 waiting time (Delay of Gratification Task) (*OR* ADHD/C vs. ADHD/I = 0.742. *OR* ADHD/C vs. controls = 0.650. *OR* ADHD/I vs. controls = 0.877). • ADHD/C = ADHD/I < controls: T_1 latency to first active engagement (Forbidden Toy Situation) (*OR* ADHD/C vs. controls = 0.995. *OR* ADHD/I vs. controls = 0.996). T_3 total planning efficiency score (Tower of Hanoi) (*OR* ADHD/C vs. controls = 0.901. *OR* ADHD/I vs. controls = 0.926). • ADHD/C = ADHD/I > controls T_2 omission errors (CPT) (*OR* ADHD/C vs. controls = 1.051. *OR* ADHD/I vs. controls = 1.046). T_3 commission errors (CPT) (*OR* ADHD/C vs. controls = 1.051. *OR* ADHD/I vs. controls = 1.031). T_3 omission errors (CPT) (*OR* ADHD/C vs. controls = 1.085. *OR* ADHD/I vs. controls = 1.076). • ADHD/C > ADHD/I = controls: T_2 commission errors (CPT) (*OR* ADHD/C vs. controls = 1.021. *OR* ADHD/C vs. ADHD/I = 1.016). • Other predictor effects were not significant.
P & T DSM-III-R interview/questionnaires[e].	
P & C DSM-IV semi-structured interview: • 44 ADHD full persisters • 29 ADHD full remitters • 85 Controls → ADHD full persisters and ADHD full remitters were contrasted with controls, but not with each other.	• Full persisters and full remitters > controls T_1 *SD* of RT (CPT). • Full persisters < controls T_1 WMI scores (WAIS-III). T_1 number of correct responses (CPT). T_1 RT (CPT). • Full persisters > controls T_1 commission errors (CPT). • Full remitters < controls T_1 word-reading scores (Stroop Color Word Test).

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
		(88 % boys in complete sample)		- WAIS-III Arithmetic, Digit Span, Letter-Number Sequencing (working memory measured by an aggregated measure of standard scores (WMI)) - WAIS-III Digit Symbol/Coding , Symbol Search (processing speed measured by an aggregated measure of standard scores (PSI)) - Stroop Color Word Test (basic processing speed measured by word-reading score, color-naming score, and interference control measured by interference score) -CPT (inhibition measured by commission errors – stability of temporal processing measured by *SD* or RT - alerting attention measured by mean reaction time (RT) and correct responses)
10. Wåhlstedt, Thorell, & Bohlin, 2008				
Type-c study $N_0 \rightarrow B_1$	T_0 Baseline	87 children derived from random population sample (206 children (103 boys)) on basis of EF scores and ADHD symptoms (T questionnaires).	Not reported.	- Stroop-like task, verbal WM task, spatial WM task and verbal fluency (groups divided in 'good EF' versus 'poor EF' based on their scores on these four tasks)
	T_1 2 year follow-up	Same as baseline (no attrition)	ADHD: 6.3 year (*SD* = 9.4 m) ADHD + poor EF: 6.9 year (*SD* = 9.4 m) Poor EF: 6.0 year (*SD* = 8.8 m) Controls: 7.1 year (*SD* = 7.9 m)	No measurements
11. Brocki, Nyberg, Thorell, & Bohlin, 2007				
Type-c study $N_0 \rightarrow B_2$ $N_1 \rightarrow B_2$	T_0 Baseline	72 children (60 boys). 1/3 from clinical sample and 2/3 from random population sample chosen to be proportional to clinical	5.4 year (*SD* = 0.69)	- Stroop-like task + Knock and Tap subtest NEPSY (interference control measured by an aggregated score of number of correct responses on both tasks) - Statue subtest NEPSY

Behavioral measures (criterion)[b]	Results
	• No other predictor effects were significant.
Composite of P and T ratings of DSM-IV criteria for: • ADHD/H symptoms • ADHD/I symptoms	After adjustment for gender, age and SES effects: • Positively predicting ADHD/H symptoms: T_0 poor EF and little ADHD symptoms (vs. controls: η^2=.07). T_0 poor EF and more ADHD symptoms (vs. controls: η^2=.12). • Positively predicting ADHD/I symptoms: T_0 poor EF (vs. good EF: η^2=.05). T_0 poor EF and little ADHD symptoms (vs. controls: η^2=.16). T_0 poor EF and more ADHD symptoms (vs. controls: η^2=.18). • Other predictor effects were not significant.

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
		sample in terms of gender and age.		(interference control measured by number of intervals) - Go/No-Go task (inhibition measured by commission errors) - Pig Sty (spatial working memory measured by total points) - Wordspan forward (verbal working memory measured by total points forward) - Wordspan backward (verbal working memory measured by total points backward)
	T_1 12-18 month follow-up	Not reported	6.3 year (*SD* = 0.68)	- WISC-III Block Design + Information (IQ measured by an aggregated measure of standard scores (TIQ))
	T_2 26 month follow-up (*SD* = 0.28)	7 children dropped out leaving 65 children for follow-up.	7.5 year (*SD* = 0.47)	No measurements
12. Fischer, Barkley, Smallish, & Fletcher, 2005				
Type-a study $N_{1\text{-}2} \rightarrow B_{0\text{-}2}$ Type-b study $N_2 \rightarrow B_{0\text{-}2}$	T_0 Baseline	158 hyperactive children. Clinical sample. 81 controls. Community sample.	n.a. (4 – 12 year)	No measurements
	T_1 8 year follow-up	Not reported	n.a. (12-20 year)	- CPT (inhibition and alerting attention measured by commission errors and omission errors respectively)
	T_2 +/- 12 year follow-up	37 originally hyperactive children and 11 controls with incomplete data dropped out.	21 year (19 - 25 year)	- WAIS-III Vocabulary and Block Design (IQ measured by an aggregated measure of standard scores (TIQ)) - CPT (same as $T_{1)}$ - Cancellation Task (inhibition and alerting attention measured by commission errors and omission errors respectively) - Card Playing Test

Behavioral measures (criterion)[b]	Results
P and T ratings of DSM-IV criteria for: • ADHD symptoms (mean score of ADHD/H and ADHD/I)	After adjustment for age and social background effects: • Positively predicting ADHD symptoms: T_0 commission errors (Go/No-Go Task) (r = .39). • Negatively predicting ADHD symptoms: T_0 aggregated score of number of correct responses (Stroop-like task + Knock and Tap subtest) (r = -.48). T_0 number of intervals (Statue subtest) (r = -.45). T_1 TIQ (WISC-III Block Design and Information) (r = -.32). • Other predictor effects were not significant.
P questionnaires combined with additional information, highly likely fulfilling ADHD DSM-III-R criteria.	
C DSM-IV structured interview: • 68 ADHD full persisters • 53 ADHD full/partial remitters • 70 controls	• Full persisters = full/partial remitters = controls: $T_{1\text{-}2}$ development of omission and commission errors (CPT). • Full persisters = full/partial remitters < controls: T_2 TIQ (WAIS Vocabulary and Block Design). • Full persisters > controls: T_2 omission and commission errors (CPT). • Other predictor effects were not significant.

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
				(inhibition measured by number of cards and earnings)
13. Kalff et al., 2005				
Type-c study $N_1 \rightarrow B_2$	T_0 Baseline	452 children derived from a random population sample on basis of CBCL scores.	Not reported.	
	T_1 4 month follow-up	52 children with incomplete data dropped out leaving 400 children for follow-up.	Not reported.	- ANT Baseline Speed Task (basic processing speed measured by reaction time (RT) (ms) – alerting attention measured by mean percentage of errors – stability of temporal processing measured by *SD* of RT) - ANT Sustained Attention Task (alerting attention measured by reaction time (RT) (ms) and mean percentage of errors - stability of temporal processing measured by *SD* of RT) - ANT Divided Attention Task - ANT Focused Attention Task (for both tasks: orienting attention measured by reaction time (RT) (ms) and mean percentage of errors - stability of tempor2al processing measured by *SD* of RT) - ANT Go/No-Go Task (inhibition measured by mean percentage of commission errors - alerting attention measured by RT (ms) and mean percentage of omission errors - stability of temporal processing measured by *SD* of RT)
	T_2 18 month follow-up	89 children with incomplete data dropped out leaving 363 children (205 boys) for follow-up.	About 7-8 years	

Behavioral measures (criterion)[b]	Results
Assignment to one of following groups based on P structured DSM-IV[e] interview: • 33 ADHD • 75 borderline ADHD • 122 pathological controls • 133 healthy controls Simple contrasts were made with ADHD as the reference group.	Results were comparable after adjustment for baseline speed. • ADHD > healthy controls: T_1 RT (Baseline Speed, Divided Attention, Focused Attention,). T_1 *SD* (Baseline Speed, Divided Attention, Focused Attention, Go/No-Go). T_1 percentage of omission errors (Go/No-No). • ADHD > pathological controls: T_1 RT (Baseline Speed, Focused Attention). T_1 *SD* (Baseline Speed, Divided Attention, Focused Attention). T_1 percentage of omission errors (Go/No-Go). • ADHD > Borderline ADHD: T_1 *SD* (Divided Attention). • Other predictor effects were not significant

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
14. Berlin, Bohlin, & Rydell, 2003				
Type-c study $N_0 \rightarrow B_1$ $N_0 \rightarrow B_2$	T_0 Baseline	151 children (53 boys). Random population sample.	5.3 year (*SD* = 1.12 m)	- Go/No-Go Task (inhibition measured by commission errors)
	T_1 3 year follow-up	16 children dropped out leaving 135 children for follow-up.	8.0 year (*SD* = 2.4 m)	No measurements
	T_2 3.5 year follow-up	6 children dropped out leaving 129 children for follow-up	8.7 year (*SD* = 1.6 m)	No measurements
15. Kalff et al., 2002				
Type-c study $N_1 \rightarrow B_2$	T_0 Baseline	443 children (252 boys) derived from random population sample on basis of CBCL.	Not reported.	No measurements
	T_1 4 month follow-up	Same as baseline (no attrition)	6.2 year (5.4 -7.8 year, *SD* = 0.45)	- RAKIT Embedded Figures (visual processing measured by number of correct drawings) - RAKIT Verbal Fluency (verbal fluency measured by number of words) - RAKIT Vocabulary subtest (IQ, not stated which variable exactly is used.) - K-ABC Gestalt Closure (visual processing measured by number of correct pictures) - K-ABC Number Recall (verbal working memory measured by number of digits) - K-ABC Word Order (verbal working memory measured by number of pictures in correct order) - Progressive Figures Test (Set shifting measured by time to finish) - VMI Beery (visual processing measured by number of correctly drawn forms)

Behavioral measures (criterion)[b]	Results
T ratings of DSM-IV criteria for: • ADHD/H symptoms at school • ADHD/I symptoms at school	• Positively predicting ADHD/H and ADHD/I symptoms: T_0 commission errors (Go/No-Go) (ADHD/H: r = .41. ADHD/I: r = .38).
T ratings of DSM-IV criteria for: • ADHD/H symptoms at home • ADHD/I symptoms at home	• Positively predicting ADHD/H and ADHD/I symptoms: T_0 commission errors (Go/No-Go) (ADHD/H: r = .25. ADHD/I: r = .35 respectively). • Other predictor effects were not significant.

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
	T_2 18 month follow-up	77 children with incomplete data dropped out leaving 366 children for follow-up (208 boys)	7.1 year (*SD* = 0.39)	No measurements
16. Marakovitz & Campbell, 1998				
Type-c study $N_0 \rightarrow B_2$ $N_1 \rightarrow B_2$	T_0 Baseline	112 boys. Subsample from random population sample on basis of ADHD checklist plus matched controls.	3.8 year (2.4 – 4.8 year)	- Resistance to Temptation Task (reward delay aversion measured by latency to touch) - Delay of Gratification Task (reward delay aversion measured by impulsive responses)
	T_1 2 year follow-up	12 boys with incomplete data dropped out leaving 100 boys for follow-up.	5.9 year (4.4 – 7.2 year)	- CPT (inhibition and alerting attention measured by commission and omission errors respectively) - MFF (inhibition measured by latency to first response)
	T_2 5 year follow-up	In sum 17 boys with incomplete data dropped out leaving 85 boys for follow-up.	n.a. (6.5 – 11.4 year)	
17. Biederman et al. 1996				
Type-b study $N_0 \rightarrow B_{0\text{-}1}$	T_0 Baseline	260 boys. clinical and random (controls) population sample.	n.a. (6 - 17 year)	- WISC Vocabulary, Block Design (IQ measured by an aggregated measure of standard scores (TIQ))
	T_1 4 year follow-up	33 children with incomplete data dropped out leaving 237 children for follow-up.	Not reported.	- Same as baseline

Behavioral measures (criterion)[b]	Results
Assignment to one of following groups based on P structured DSM-IV interview[e] : • 33 ADHD • 75 borderline ADHD • 258 controls	• Borderline ADHD < controls: T_0 IQ (RAKIT Vocabulary subtest). • Other predictor effects were not significant. After adjustment for gender, age, parental occupation, IQ and CBCL group assignment effects: • ADHD < controls T_1 number of correct drawings (RAKIT Embedded Figures). T_1 number of pictures in correct order (K-ABC Word Order). T_1 number of correctly drawn forms (VMI Beery). • Borderline ADHD < controls T_1 number of correct drawings (RAKIT Embedded Figures). • More time to finish (Progressive Figures Test) at T_1 differentiated ADHD, Borderline ADHD and No ADHD[f]. • Other predictor effects were not significant.
P DSM-III-R structured diagnostic interview: • 23 ADHD/I • 40 non-ADHD/I[g] • 34 controls	• ADHD/I < controls T_0 latency to touch (Resistance to Temptation Task). T_1 latency to first response (MFF). • Non-ADHD/I < controls T_1 latency to first response (MFF). • Other predictor effects were not significant.
P and C structured DSM-III-R interviews: • 140 boys with ADHD • 120 controls Assignment to one of following groups based on P and C structured DSM-III-R interview: • 109 ADHD full/partial persister • 9 ADHD full remitter (late)	After adjustment for age and baseline GAF score effects: • No predictor effects were found.

Table 2.1. Continued.

Study design[a]	Follow-up period	Participants and selection procedure	Mean age (age range, *SD*)	Neurocognitive measures (measurement potential; dependent variable)
18. Hart, Lahey Loeber, Applegate, & Frick 1995				
Type-b study $N_0 \rightarrow B_{0\text{-}1}$	T_0 Baseline	177 boys. Clinical sample.	n.a. (7 - 12 year)	- WISC-R (IQ measured by an aggregated measure of standard scores (FSIQ)
	T_1 4 year follow-up	6 boys dropped out leaving 171 boys for follow-up.		No measurements

Note. ADHD = Attention Deficit Hyperactivity Disorder; ADHD/C = Attention Deficit Hyperactivity Disorder/Combined subtype; ADHD/H = Attention Deficit Hyperactivity Disorder/Hyperactive-impulsive subtype; ADHD/I = Attention Deficit Hyperactivity Disorder/Inattentive subtype; ANT = Amsterdam Neuropsychological Tasks; C = child; CBCL = Child Behavior Checklist; CPT = Continuous Performance Task; CVLT = California Verbal Learning Test; DS = Digit Span; DSM (-III-R) = Diagnostic and Statistical Manual of Mental Disorders (3rd edition-revised); DSy/Co = Digit Symbol/Coding; EF = Executive Functioning; FFD = Freedom from Distractibility; FSIQ = Full Scale Intelligence Quotient; K-ABC = Kaufman Assessment Battery for children; KHM = Kaufman Hand Movements Test; m = month(s); MMF = Matching Familiar Figures Test; n.a. = not assessed; NEPSY = Developmental Neuropsychological Assessment Battery; POI = Perceptual Organization Index; RAKIT = Revised Amsterdam Child Intelligence Test; ROCF = Rey-Osterrieth Complex Figure; SES = socioeconomic status SRCT = Stimulus and Response Conflict Tasks; SS = Symbol Search; T = Teacher; TIQ = total intelligence quotient; P = Parent; PSI = Processing Speed Index; VCI = Verbal Comprehension Index; VMI Beery = Developmental Test of Visual-Motor Integration; WAIS-III = Wechsler Adult Intelligence Scale-III; WAIS-III-R = WAIS-III − Revised; WCST = Wisconsin Card Sorting Test; WISC = Wechsler intelligence Scale for Children; WISC-R = Wechsler intelligence Scale for Children − Revised; WM = working memory; WMI = Working Memory Index.
[a] The predictive relation investigated in each study is provided in this column. N = neurocognition and B = behavior. Subscripts show at which time point N or B were assessed, with '0' representing baseline measurement. N_0-N_1 means 'the development of neurocognition from T_0 to T_1' The same applies to B_0-B_1 for example. [b] Definitions of ADHD persistence or remittance are based on definitions that were used in included studies. (I) Cases meeting full ADHD DSM criteria at follow-up are referred to as 'ADHD full persisters'. (II) Cases meeting either full or subthreshold criteria for ADHD at follow-up are referred to as 'ADHD full/partial persisters', defined as meeting *at least* three or four symptoms of hyperactivity/impulsivity or inattention with significant impairment. This symptom threshold varies across studies. Thus, studies reporting on ADHD full/partial persisters did not distinguish between cases meeting full diagnostic criteria for ADHD and cases meeting only subthreshold criteria. (III) Cases meeting less than four or three symptoms of hyperactivity/impulsivity or inattention at follow-up are referred to as 'ADHD full remitters'. (IV) Cases that did not meet full criteria for ADHD at follow-up were referred to as 'ADHD full/partial remitters', containing both fully remitted cased as well as ADHD subthreshold cases. Thus, there is overlap between the ADHD full/partial persisters group (II) and the ADHD full/partial remitters group (IV), since both groups contain children meeting subthreshold criteria at follow-up. [c] See text for a full description of the different study designs. [d] Not clear which number exactly was included in relevant analyses. [e] Authors claimed that the ADHD classification is highly comparable with *DSM-IV* criteria. [f] Group main effect was not further tested because of too large differences in variance. [g] Children in the non-ADHD/I group had no diagnosis of ADHD at follow-up, but were recruited at baseline measurement as 'problem boys', with elevated levels of hyperactivity, inattentive problems or non-compliance. [h] Moderate full/partial remitters met full/partial ADHD remitting criteria three *or* four years after baseline measurement, and met full ADHD criteria at the other of these two measurements.

Behavioral measures (criterion)[b]	Results
• 10 ADHD full remitter (early) • 109 Controls P, C and T structured DSM-III-R interview.	
Assignment to one of following groups based on P, C and T structured DSM-III-R interview: • 75 ADHD full persister • 22 ADHD moderate full/partial remitter[h] • 9 ADHD full/partial remitter • 19 controls	• No predictor effects were found.

with persisting symptoms. However, studies are cross-sectional in design, not investigating the developmental aspects. In the light of testing the model of Halperin & Schulz, we consider cognitive control as 'higher order' neurocognitive functions.

Inhibition. Inhibition is the ability to suppress an ongoing dominant response (Nigg, 2000). Measures of inhibition used in the included studies of this review (see Table 2.1) are commission errors on the Continuous Performance Task (CPT), the Go/No-Go Task, and the Cancellation Task; number of cards, and earnings on the Card Playing Test; latency to first response on the Matching Familial Figures Test (MFF). Two type-a studies investigated the predictive value of inhibition (Vaughn et al., 2011; Fischer et al., 2005). Results showed that inhibition did not predict symptom change in children with and without ADHD (Vaughn et al., 2011), and inhibition in childhood did not differentiate between young adult persistence, remittance, or control status (Fischer et al., 2005). In other words, all three groups (persisters, remitters, and controls) showed the same developmental pattern of inhibition. Two type-b studies reported on *current* inhibition in young adulthood (Fischer et al., 2005; Halperin et al., 2008). There was no evidence for differences between persisters and remitters (Fischer et al., 2005). Both studies showed similar levels of current inhibition for remitters and controls, while persisters performed worse than controls on two out of five measures of inhibition (Fischer et al., 2005; Halperin et al., 2008). As indicated earlier, Halperin et al. (2008) did not compare ADHD persisters and remitters because of limited group numbers. Type-c studies (five out of six) showed that inhibition in childhood predicted future ADHD symptoms or diagnosis assessed still in childhood (Berlin et al., 2003; Brocki et al., 2010; Brocki et al, 2007; Campbell & von Stauffenberg, 2009; Marakovitz & Campbell, 1998), although this was not true for all measures of inhibition (Brocki et al., 2010; Marakovitz & Campbell, 1998). One of six studies showed that inhibition was no significant predictor for ADHD diagnosis assessed still in childhood (Kalff et al., 2005).

Interference control. Interference control is another measure of cognitive control slightly different from inhibition. Interference control is the ability to suppress a *distractive* stimulus or response option that might slow a primary response (Nigg, 2000). Measures of interference control that were used are interference score on the Stroop Color Word Test; reaction time (RT) and accuracy on the Stimulus and Response Conflict Task (SRCT); number of correct responses on both a Stroop-like task and the Knock and Tap Test; number of intervals on the Statue Subtest. Three type-b studies investigated *current* interference control in (young) adulthood in persisters, remitters, and controls (Barkley & Fischer, 2011; Bédard et al., 2010; Halperin et al., 2008). One study showed that persisters performed worse than remitters (Barkley & Fischer, 2011). In one study, remitters performed worse than controls (Bédard et al., 2010), and in two studies, persisters performed worse than controls as well (Barkley & Fischer, 2011; Bédard et al., 2010). Type-c studies (two out of two) showed predictive

value for ADHD symptoms in young children, with somewhat larger effect sizes at one year (Brocki et al., 2010) than at two year follow-up (Brocki et al., 2007).

Working memory. Working memory refers to the ability to temporarily maintain and manipulate information necessary for achieving a certain goal (Baddeley, 2003). Measures of working memory that were used are the Digit Span scaled score (WISC/WAIS); the Digit Span forwards and backwards combined raw score (WAIS); the Working Memory Index (WAIS); number correct and longest sequence completed on the Kaufman Hand Movement Test (KHM); the longest correctly reproduced sequence on the Simon game, total number of pairs ordered correctly on the Children's Size-Ordering Task (CSOT); number of pictures in correct order on the Kaufman-ABC (K-ABC) Word Order; total points forward and total points backward on a Wordspan task; number of digits on the K-ABC Number Recall; total points on the Pig Sty Task. One out of one type-a study did not differentiate between persisters, remitters or controls based on the development of verbal working memory from childhood/adolescence into (young) adulthood (Biederman, Petty, Ball et al., 2009). One type-b study investigated *early* working memory performance in late childhood and adolescence, for outcome in adulthood (Biederman, Petty, Ball et al., 2009). Remitters and persisters showed similar levels of verbal working memory, and both ADHD groups performed worse than controls, independent from the time of measurement (Biederman, Petty, Ball et al., 2009). Three type-b studies investigated *current* working memory abilities in (young) adulthood (Barkley & Fischer, 2011; Biederman, Petty, Ball et al., 2009; Halperin et al., 2008). Two studies showed that current verbal and non-verbal working memory did not differentiate persisters and remitters (Barkley & Fischer, 2011; Biederman, Petty, Ball et al., 2009). Two studies also showed that remitters performed worse than controls (Barkley & Fischer, 2011; Biederman, Petty, Ball et al., 2009). In addition, three studies differentiated persistence from control status (Barkley & Fischer, 2011; Biederman, Petty, Ball et al., 2009; Halperin et al., 2008). Three type-c studies showed mixed results. One study found predictive value of early verbal working memory still in childhood, but only for the inattentive type (ADHD/I), not for the hyperactive type (ADHD/H) (Brocki et al., 2010). In a second study, one of two measures of verbal working memory predicted ADHD diagnosis in early childhood (Kalff et al., 2002), and another study showed no evidence for the predictive value of early verbal working memory as well as non-verbal working memory on ADHD symptoms (Brocki et al., 2007).

Set-shifting. Set-shifting is the ability to rapidly alternate between mental sets. One measure of set-shifting was used: time to finish on the Progressive Figures Test. One out of one type-c study found that the ability to shift in young children differentiated ADHD diagnosis, borderline ADHD (children meeting symptomatic criteria but not meeting the criteria of impairment), and controls one year later (Kalff et al., 2002).

Planning. Planning is the ability to sequence and control behavior, and take certain precautions in order to achieve a specified goal (Unterrainer & Owen, 2006). Measures of planning that were used are total score, number of correct to first trial, and time to first move on the Tower of London (ToL); and total planning efficiency score on the Tower of Hanoi (ToH). One type-b study investigated *current* planning measures in adulthood, and showed that persisters, remitters and controls were not differentiated from each other on current planning measures (Barkley & Fischer, 2011). One out of one type-c study showed that in young children, planning abilities predicted ADHD diagnosis two years later (Campbell & von Stauffenberg, 2009). In that study the inattentive type (ADHD/I) and combined type (ADHD/C) were differentiated from controls, but not from each other.

Fluency. Fluency refers to the ability to quickly generate responses (solutions) to a certain problem (Pennington & Ozonoff, 1996). Measures of fluency were number of unique designs from the Five-Points Test of Design Fluency; and number of words from the RAKIT verbal fluency subtest. One type-b study investigated *current* (non-verbal) fluency, and showed that current fluency did not differentiate persisters from remitters in adulthood, and both ADHD groups were differentiated from controls (Barkley & Fischer, 2011). One out of one type-c study showed that verbal fluency did not predict ADHD diagnosis in very young children one year later (Kalff et al., 2002).

Aggregated executive functioning. Since cognitive control is closely linked to the concept of EF (Dramsdahl, Westerhausen, Haavik, Hugdahl, & Plessen, 2011), these findings are outlined here as well. Table 2.1 shows details of the measures that were used for the aggregated EF measures. For instance, one of the studies used performance on four different tasks (Stroop-like task, verbal WM task, spatial WM task, and verbal fluency) to divide groups in 'good EF' versus 'poor EF'. Poor EF was defined as scoring in the lowest 30% on at least two tasks, and good EF was defined as scoring in the highest 50% on all four tasks (Wåhlstedt et al., 2008). Together, four studies investigated the predictive value of aggregated EF measures (Biederman, Petty, Ball et al., 2009; Halperin et al., 2008; Mick et al., 2011; Wåhlstedt et al., 2008). One type-a study investigated the predictive value of the development of an aggregated measure of EF from childhood to adulthood, and found no differences between persistence, remittance, and control status (Biederman, Petty, Ball et al., 2009). Two type-b studies investigated the predictive value of *early* aggregated EF measures in young adulthood (Biederman, Petty, Ball et al., 2009; Mick et al., 2011). Both studies showed that an aggregated EF measure did not differentiate persisters from remitters in adolescence and in young adulthood, and both ADHD groups were different from controls (Biederman, Petty, Ball et al., 2009; Mick et al., 2011). Three type-b studies investigated *current* measures of aggregated EF in (young) adulthood (Biederman, Petty, Ball et al., 2009; Halperin et al., 2008; Mick et al., 2011), and reported similar effects as for early measures of aggregated EF; two studies showed

that persisters and remitters did not differ from each other (Biederman, Petty, Ball et al., 2009, Mick et al., 2011). In two studies, both ADHD groups performed worse than controls (Biederman, Petty, Ball et al., 2009; Mick et al., 2011), while in the third study persisters and remitters were not differentiated from controls (Halperin et al., 2008). One out of one type-c study showed predictive value for an aggregated EF measure on both ADHD/I symptoms and ADHD/H symptoms compared to control status in early childhood (Wåhlstedt et al., 2008).

Summarizing the different subdomains of cognitive control, none of three type-a studies predicted ADHD (symptom) persistence (inhibition, working memory, aggregated EF): the development of cognitive control abilities was similar for persisters, remitters, and controls. None of two type-b studies investigating *early* cognitive control measures differentiated persisters from remitters, and both persisters and remitters were differentiated from controls (early measures of working memory, aggregated EF). Six type-b studies investigated *current* cognitive control measures. In only one of these studies persisters were differentiated from remitters; four studies differentiated ADHD remitters from controls (interference control, working memory, fluency, and aggregated EF), and all six studies differentiated persisters from controls. The majority of measures in eight type-c studies showed that cognitive control capacities (inhibition, interference control, set-shifting, planning, and aggregated EF) in early childhood predict future ADHD symptoms or diagnosis (still in childhood). However, verbal and non-verbal working memory was not predictive in five out of seven measures.

Reward Processing

Reward processing refers to the sensitivity to reinforcement which influences the degree of motivation to perform and is related to orbito-fronto-striatal loops as described above (Brenhouse & Andersen, 2011; Durston et al., 2011). It also refers to the processing of delayed rewards, which relies on ventral fronto-striatal circuits (Sonuga-Barke et al., 2010). The activation of these circuits is quite different in adolescents and adults, suggesting these systems do not mature before adolescence (Casey et al., 2011). At the behavioral level, it is known that children with ADHD have a stronger preference for smaller immediate rewards over larger delayed rewards compared to controls. In addition, it appeared that the positive effect of reward contingencies on task performance is somewhat more prominent in children with ADHD than in control children (Luman, Oosterlaan, & Sergeant, 2005). Although literature on reward processing in adults is scarce, evidence suggests that adults with ADHD show reward delay aversion compared to controls (Marx et al., 2010). This is in line with findings of similar neurobiological dysfunctions of reward processing in adolescents (Scheres, Milham, Knutson, & Castellanos, 2007) and in adults with

ADHD (Plichta et al., 2009; Ströhle et al., 2008). All three studies showed reduced ventral striatal activity in ADHD compared to controls during reward anticipation in a reinforcement reaction time task, indicating that problems with reward processing are present at least in persistent ADHD cases. For the purpose of this review, we consider reward processing as a lower order neurocognitive function.

Measures of reward processing (reward delay aversion) that were used are latency to first active engagement on a Forbidden Toy Situation; waiting time on a Delay of Gratification Task (choosing between a small immediate reward or a larger reward seven minutes later); impulsive responses on another Delay of Gratification Task (waiting for a signal before searching for a cookie hidden under one of three cups); and latency to touch on a Resistance to Temptation Task. Results of type-c studies (two out of two) showed predictive value of reward delay aversion for future ADHD/C and ADHD/I compared to control status, still in childhood (Campbell & von Stauffenberg, 2009; Marakovitz & Campbell, 1998), although one measure in the Marakovitz & Campbell study showed no predictive value.

Temporal Processing

Temporal processing is a very broad term which has been used to refer to the ability to order and predict sequential events in time, and show temporal stability of responding (Durston et al., 2011); skills that depend on intact time perception, time discrimination and time (re)production (Castellanos & Tannock, 2002; Ivry, 1996). Even though these processes are quite different and probably reflect diverse neurobiologial mechanisms, they all rely at least partially on fronto-cerebellar circuits (Castellanos & Tannock, 2002; Durston et al., 2007; Durston et al., 2011) with the cerebellum as key player (Mackie et al., 2007). The cerebellum appears to increase further in size during adulthood, especially the vermis (Durston et al., 2001) and thus is not a fully matured structure yet early in life. Deficits in different types of temporal processing not only exist in children with ADHD (time discrimination, time reproduction (Rommelse, Altink, Oosterlaan et al., 2008; Rommelse, Oosterlaan et al., 2007; Toplak, Dockstader, & Tannock, 2006); predicting sequential events in time (Durston et al., 2007)) but also in adults with ADHD (time estimation and reproduction (Barkley, Murphy, & Bush, 2001; Marx et al., 2010). Increasing cerebellar dysfunction (again particular in vermal areas) appears during adolescence in children with ADHD relative to normally developing children (Mackie et al., 2007). It is thus suggested that, based on cross-sectional studies, temporal processing deficits are apparent in at least persisting ADHD cases. In terms of testing the Halperin & Schulz model, we consider temporal processing as a lower order neurocognitive function.

Studies into temporal processing are limited to studies using measures of temporal stability (e.g., RT variability). In all studies the SD of RT (SDRT) was used, derived from the CPT, SRCT interference control and inhibition conditions, the Go/No-Go Task, a Divided Attention Task and a Sustained Attention Task. One type-a study investigated the predictive value of the development of RT variability from middle to late childhood, and found no predictive value for ADHD symptom change (Vaughn et al., 2011). Two type-b studies investigated *current* RT variability in young adulthood (Bédard et al., 2010; Halperin et al., 2008). There was no evidence for differences between persisters and remitters (Bédard et al., 2010). One study showed that remitters were differentiated from controls (Halperin et al., 2008), and both studies differentiated persisters from controls (Bédard et al., 2010; Halperin et al., 2008). One type-c study showed predictive value for future ADHD diagnosis (ADHD versus control status) one year later for four out of five measures of RT variability (Kalff et al., 2005).

Intelligence

Another domain potentially relevant in ADHD research is intelligence. Intelligence indicates a general mental capability encompassing a wide range of cognitive abilities including, for example, reasoning, planning, problem solving and abstract thinking. Here we will focus on the most commonly used division between verbal and performance intelligence (Wechsler, 1997). There is no defined brain network subserving intelligence since intelligence is a heterogeneous concept, but of interest is that the developmental maturation of cortical thickness appears to be related to intelligence; a faster, but later maturation is related to higher intelligence levels (Shaw et al., 2006). Children show an increase in verbal and performance intelligence over time until adulthood, with the steepest increases seen in childhood (Waber et al., 2007). In children with ADHD, and to a somewhat lesser extent in adults with ADHD, lower intelligence has been robustly reported (Bridgett & Walker, 2006; Frazier et al., 2004; Hervey, Epstein, & Curry, 2004; Schoechlin & Engel, 2005), with larger effect sizes for verbal than for performance IQ, suggesting this to be a stable trait in at least persistent ADHD cases. Intellectual functioning involves both higher level neurocognitive functioning as more basic lower level functions (e.g. basic information processing speed), depending on which subtest measure of IQ is used (for example full scale IQ [FSIQ]), of which processing speed is a part, versus Block Design as a measure of Performance IQ (PIQ).

Measures of intelligence that were used are Total IQ (TIQ, estimated from Vocabulary or Information, and Block Design, sometimes supplemented with other subtests of the WISC or WAIS), FSIQ (using all subtests of an intelligence scale); PIQ (estimated from Block Design of the WISC or WAIS), Verbal IQ (VIQ, estimated from Vocabulary of

the WISC or WAIS, estimated from Verbal Comprehension Index from the WAIS, or estimated from Vocabulary from the RAKIT); and Freedom from Distractibility Index (FFD), from WISC/WAIS subtests Arithmetic and Digit Symbol Coding). One type-a study investigated the predictive value of the development of PIQ and VIQ from childhood/adolescence into (young) adulthood, and showed no predictive value of the decrease in PIQ for differentiating persisters from remitters (Biederman, Petty, Ball et al., 2009). Both ADHD persisters and remitters were differentiated from controls (Biederman, Petty, Ball et al., 2009). Persisters, remitters and controls all showed a similar increase in VIQ (Biederman, Petty, Ball et al., 2009). Results of Total IQ should be taken with some caution, since PIQ and VIQ showed different results (see Table 2.1 for results on TIQ) (Biederman, Petty, Ball et al., 2009). Six type-b studies investigated *early* measures of IQ in childhood and adolescence (Bédard et al., 2010; Biederman et al., 1996; Biederman, Petty, Ball et al., 2009; Hart et al., 1995; Langley et al., 2010; Mick et al., 2011). There was no evidence for differences between adolescent or young adult persisters and remitters. Two of six studies differentiated both ADHD persisters and remitters from controls in adolescence and young adulthood (Biederman, Petty, Ball et al., 2009; Mick et al., 2011), while the other four studies did not differentiate persisters and remitters from controls, or did not predict ADHD symptom change (Bédard et al., 2010; Biederman et al., 1996; Hart et al., 1995; Langley et al., 2010). Four studies investigated *current* measures of IQ in adolescence or (young) adulthood (Barkley et al., 2011; Biederman, Petty, Ball et al., 2009; Halperin et al., 2008; Mick et al., 2011). Similarly, no studies differentiated persisters from remitters (Barkley et al., 2011; Biederman, Petty, Ball et al., 2009; Mick et al., 2011). Three studies differentiated persistence and remittance from control status (Barkley et al., 2011; Biederman, Petty, Ball et al., 2009; Mick et al., 2011), while one study did not differentiate persisters and remitters from controls (Halperin et al., 2008). Three type-c studies showed mixed findings. One study demonstrated that IQ was predictive for future ADHD symptoms in very young childhood (Brocki et al., 2007). In another study, only the borderline ADHD group was differentiated from controls using IQ, while children with ADHD performed similar to controls (Kalff et al., 2002). In one study, IQ measured in childhood did not predict ADHD at follow-up in adolescence (Langley et al., 2010).

Attention

Another neurocognitive domain that plays an important role in ADHD is attention. Although consensus lacks, a large body of literature distinguishes between three sub-domains of attention including alerting, orienting and executive attention (Posner & Petersen, 1990; Raz & Buhle, 2006). Alerting can be defined as the ability to attain and maintain a state of high sensitivity in anticipation of a stimulus. This alertness or vigilance is required to react without delay to an impending stimulus (Posner, 2008;

Raz & Buhle, 2006), and is thought to be mediated by frontal and (inferior) parietal regions, as well as the locus coeruleus (Raz, 2004; Raz & Buhle, 2006). Orienting allows the selection of information from sensory input, sometimes also referred to as 'scanning' or 'selection' (Posner, 2008; Raz & Buhle, 2006) and is thought to rely on both subcortical structures (e.g. part of thalamus) and cortical structures (superior parietal lobe, frontal eye fields and temporo-parietal junction) (Raz, 2004; Raz & Buhle, 2006). Executive attention is often equated to interference control and is discussed within the section on cognitive control. Normal maturation of the attentional networks appears to continue after childhood, since between the age of 12 years and adulthood these brain areas are matured (Konrad et al., 2005). This is in line with behavioral developmental studies (Konrad et al., 2005; Rueda et al., 2004). In adults with ADHD, functional and structural brain deficits as well as phenotypic expression of attentional problems related to alerting, orienting and executive attention are still present, although possibly to a lesser extent than in children with ADHD (Amico, Stauber, Koutsouleris, & Frodl, 2011; Cubillo et al., 2011; Rubia, 2011; Tucha et al., 2008). Although these findings suggest that at least some aspects of attention remain impaired in some persistent ADHD cases, these studies were cross-sectional in design. We think alerting attentional tasks require little mental effort and are considered as tapping automatically controlled, lower level functions. Attentional demands increase in orienting tasks, therefore we consider performance on orienting tasks as more consciously controlled, higher level neurocognitive functions.

Measures of alerting attention that were used are RT, omission errors, and correct responses on the CPT; omission errors on the Cancellation Task and on the Go/No-Go Task; RT and mean percentage of errors on the Baseline Speed Task. Measures of orienting attention that were used are total score on the Auditory Attention Test; RT and error measures on both the Divided Attention Task and the Focused Attention Task. Two type-a studies investigated the predictive value of the development of alerting attention (Fischer et al., 2005; Vaughn et al., 2011). There was no evidence for the predictive value for ADHD symptom change in childhood (Vaughn et al., 2011), nor for the differentiation between persisters, remitters and controls based on the development of alerting attention from adolescence into young adulthood (Fischer et al., 2005). Two type-b studies investigated *current* alerting attention capacities in young adulthood (Fischer et al., 2005; Halperin et al., 2008). There was no evidence for differences between ADHD persisters and remitters (Fischer et al., 2005). Two studies found that ADHD remitters did not differ from controls (Fischer, et al, 2005; Halperin et al., 2008). ADHD persisters were different from controls in three of four measures in the two studies (Fischer et al., 2005; Halperin et al., 2008). Three type-c studies revealed mixed findings. A large random population study showed that *alerting attention* capacities measured at two different ages predicted future diagnosis of ADHD compared to control status (Campbell & Von Stauffenberg, 2009). However, in another study only one of three measures of alerting attention predicted a diagnosis

of ADHD one year later compared to control status (Kalff et al., 2005), and another study did not differentiate at all; children with ADHD/I , children with no diagnosis of ADHD/I but other behavioral problems (attention problems and hyperactivity but not severe enough to warrant a diagnosis), and controls performed similarly on a measure of alerting attention (Marakovitz & Campbell, 1998). Regarding *orienting* attention, two out of two type-c studies showed predictive value for orienting attention; in one study early orienting attention predicted future ADHD symptoms (Brocki et al., 2010), and two out of four orienting attention measures predicted future ADHD diagnosis, still in childhood (Kalff et al., 2005).

Visual Information Processing

Visual information processing can be defined as the capacity to integrate visual input from the outside world into something meaningful (Barkley, 1997). Visual processing capacities rely substantially on a connection between the occipital and temporal lobes. This so-called 'ventral stream' is activated when judging 'what' an object is. The dorsal stream, linking the occipital lobe and the parietal lobe, is activated when judging 'where' an object is, and has more to do with action regarding the object (Goodale & Milner, 1992; Goodale & Westwood, 2004). It appears that visual processing normally improves during childhood (Williams et al., 2011). Research on visual processing deficits in children and adults with ADHD is scarce, with some evidence suggesting that children with ADHD may have problems with visual sensory integration in the occipital lobe compared to controls (Nazari et al., 2010) and that children and adults with ADHD may have problems with central coherence, although findings are inconsistent (Hervey et al., 2004; Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). We consider measures that were used for visual information processing in this review as higher level neurocognitive functions.

Measures of visual information processing that were used are number of correct drawings on the RAKIT Embedded Figures; number of correctly drawn forms on the Visuo-Motor Integration Beery (VMI Beery); and number of correct pictures on the K-ABC Gestalt Closure. One type-c study showed that two of the three visual processing measures differentiated future (still in childhood) ADHD diagnosis and borderline ADHD from control status (Kalff et al., 2002).

Basic Information Processing Speed

Basic information processing speed is defined as the (mental) speed with which elementary cognitive tasks are executed, commonly measured by reaction time tasks

(Coyle, Pillow, Snyder, & Kochunov, 2011; Salthouse, 1996; Takeuchi et al., 2011). Depending on the particular information that is processed, different neural systems are involved in processing speed (Takeuchi et al., 2011). In general however, it appears that myelination of fiber tracts plays an important role in basic processing speed (Brenhouse & Andersen, 2011). A strong increase in myelination is seen in the first decade of life, with ongoing development into adulthood (Tau & Peterson, 2010). Behaviorally, it is found that processing speed increases during childhood and adolescence until adult ages in terms of a quadratic function (Kail & Ferrer, 2007). In general, children with ADHD are found to be slower in processing speed compared to control children (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008). With regard to adult ADHD, in one meta-analysis it was shown that adults with ADHD performed worse on measures of processing speed compared to controls (Bridgett & Walker, 2006), but this was not confirmed in another meta-analysis (Hervey et al., 2004). We consider basic information processing speed as a typically lower level neurocognitive ability that underlies many other neurocognitive functions.

Measures of basic information processing speed that were used are Digit Symbol score on the WISC/WAIS; both word-reading scores and color-naming score on the Stroop Color Word Test; Processing Speed Index on the WAIS; and RT on a Baseline Speed Task. One type-a study investigated the predictive value of the development of basic information processing speed from childhood into (young) adulthood (Biederman, Petty, Ball et al., 2009). There was no evidence for differences between ADHD persisters, remitters, and controls (Biederman, Petty, Ball et al., 2009). One type-b study investigated *early* measures of processing speed in childhood and adolescence, and showed no differences between young adult persisters and remitters (Biederman, Petty, Ball et al., 2009). In addition, both ADHD groups performed worse than controls. Two type-b studies investigated *current* basic information processing speed in young adults (Biederman, Petty, Ball et al., 2009; Halperin et al., 2008). One study showed no differences between ADHD persisters and remitters, with both remitters and persisters performing worse than controls (Biederman, Petty, Ball et al., 2009), while in the other study, both remitters and persisters did not differ from controls on a measure of current basic information processing speed (Halperin et al., 2008). One type-c study showed predictive value for future ADHD compared to control status in childhood (Kalff et al., 2005).

Summary and Discussion

The aim of this comprehensive review was to investigate the predictive value of neurocognitive functioning for persistence or remittance of ADHD diagnosis and symptoms, or future ADHD diagnosis or symptoms. We focused first, but not exclusively, on cognitive control, reward processing and temporal processing. It was predicted that children with the largest developmental improvement in functions that

rely on prefrontal functioning, such as cognitive control, or other higher level neurocognitive functions, are the ones that show remission from ADHD symptoms. This is based on the suggestion that the development of the prefrontal cortex and associated circuits, and thus the development of higher level neurocognitive functioning, compensates for non-cortical (e.g. striatal), lower level neurocognitive dysfunctions in ADHD (Halperin & Schulz, 2006). This theory suggests that core neurocognitive deficits of the disorder are those deficits that remain present in subjects with remitted ADHD symptoms, while deficits that disappear in remittent ADHD are seen as epiphenomena, and are not causally related to the disorder (Carr et al., 2006; Halperin & Schulz, 2006).

This review included eighteen studies, encompassing data from thirteen independent samples. Several main findings stand out. Overall, there is no evidence to suggest that ADHD remitters improve on cognitive control functions compared to ADHD persisters, or on other higher level neurocognitive abilities such as intellectual functioning. Both ADHD persisters and remitters, assessed at several ages, showed weaker performance than controls, although there are studies that showed smaller differences when differentiating ADHD remitters from controls compared to when ADHD persisters were differentiated from controls, on some measures (Bédard et al., 2010 Fischer et al., 2005). Findings are somewhat preliminary for lower level neurocognitive functions, because the main focus of most studies was on higher level domains. So far, a similar pattern of results was found for higher and lower level neurocognitive functions: ADHD remitters did not outgrow performance levels of persisters in terms of temporal processing, or other lower level neurocognitive functions, such as alerting attention and basic information processing speed. Our findings suggest that ADHD persisters and remitters remain equally impaired in terms of neurocognitive functioning. Interestingly, measures of both lower and higher level neurocognitive functions in early childhood were predictive for future ADHD symptoms or ADHD diagnosis a few years later. Unfortunately, to what extent these very early neurocognitive measures are able to predict future ADHD outcome in older children, for example in adolescence or even in adulthood, is not known from our review. Further studies are warranted here to unravel the relation between neurocognitive functions measured in very early childhood, development of ADHD symptoms and eventually also remittance or persistence of the disorder in adulthood. Last, no evidence was revealed to suggest specific differences in predictive value between the neurocognitive domains described.

Taking all findings together, it is clear that at this point, we cannot confirm the hypotheses postulated from the Halperin & Schulz model. In this model, several lower level neurocognitive functions were suggested as candidate core deficits in ADHD, thereby suggesting that ADHD remitters would resemble ADHD persisters in terms of these lower level neurocognitive functions, and both groups would show weaker

performance than controls. However, ADHD remitters not only performed at a similar level as ADHD persisters on lower level neurocognitive functions, both groups were also comparable in terms of higher level neurocognitive functions. So far, neurocognitive functioning appears unrelated to the developmental course of the disorder, although not all domains were extensively investigated (e.g. reward processing, temporal processing). The current findings are consistent with the observation that adults with ADHD, despite a fully developed brain, show both lower and higher order neurocognitive dysfunctions (Boonstra et al., 2005; Hervey et al., 2004; Schoechlin & Engel, 2005). Children with ADHD are suggested to show a developmental delay in brain maturation (Shaw, Eckstrand et al., 2007), indicating that during development brain structure and function would normalize. Our findings suggest that both children with persistent as well as remittent ADHD remain dysfunctional in terms of neurocognitive functioning. This suggests that a delayed brain maturation is not sufficient to explain the course of ADHD. A few studies have been performed on the predictive value of neurobiological measures for persistence of ADHD (for example functional or structural MRI measures). Normalization of the volume of the right parietal cortex accompanied clinical improvement of ADHD in adolescence (Shaw et al., 2006), and a progressive loss of cerebellar volumes is related to persistent symptoms in adolescence (Mackie et al., 2007). However, since there is no one-to-one relation between neurocognitive functions and these kind of neurobiological measures, it is unclear to what extent we can expect predictive value of neurocognitive functions from these results. Genetic markers of ADHD persistence might be helpful as well, but this type of research is still in its infancy. Three studies so far found a relation between specific alleles and a persistent course of ADHD (Biederman, Petty, Ten Haagen et al., 2009; Langley et al., 2009; Shaw, Gornick et al., 2007), and there may be differences in the genetic profiles of ADHD persisters and ADHD remitters (Franke et al., 2012).

The findings in this review have implications for theoretical models on the development of ADHD. It has been suggested that neurocognitive deficits act as intermediate factors between genetic factors and ADHD symptoms (Castellanos & Tannock, 2002; Rommelse, Altink, Martin et al., 2008; Uebel et al., 2010), implicating that neurocognitive deficits are related to the development of ADHD. The true mediating effect of these neurocognitive deficits is not yet established however, and the finding that ADHD remitters can not be differentiated from ADHD persisters, and ADHD remitters do not normalize in at least some domains of neurocognitive functioning, *despite* a decrease in ADHD symptoms, indicates that there is no one-to-one relation between neurocognitive and symptomatic development. This may lead to the very tentative conclusion that neurocognitive deficits in ADHD may be seen as epiphenomena instead of core causal deficit. In other words, neurocognitive dysfunctions may be *related* to the same etiological factors as the ADHD symptoms, but may not *mediate* between genes and behavior (Kendler & Neale, 2010; Walters &

Owen, 2007). This could explain the apparent existence of children with ADHD without any neurocognitive problems (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), the lack of association between neurocognitive dysfunctioning and severity of ADHD symptoms (Rommelse et al., 2011), and similar neurocognitive problems in affected and unaffected siblings while unaffected siblings clearly have less behavioral problems (Rommelse, Altink, Oosterlaan et al., 2008; Rommelse, Oosterlaan et al., 2007). The postulation that neurocognitive problems can be seen as epiphenomena in ADHD contrasts with the Halperin & Schulz model, that suggests that remaining symptoms are core deficits in ADHD.

But is there any predictive value of neurocognitive functioning? The studies that were performed in early childhood showed predictive value of neurocognitive functions for future ADHD. These studies, however, are only of practical value if neurocognitive functioning can explain some of the variance over and above ADHD symptoms at baseline. When failing to adjust for early ADHD symptoms, the neurocognitive functions may, at best, be viewed as a good proxy of early ADHD severity. In four of the nine studies that investigated the predictive value of *early* neurocognitive functioning on future ADHD symptoms or diagnosis, baseline behavioral characteristics were taken into account, ranging from baseline Global Assessment of Functioning (GAF-) scores to early ADHD symptoms. These studies showed that predictive value for future ADHD remains for cognitive control (inhibition, switching and planning, verbal working memory, executive functioning,), reward delay aversion, alerting attention, and visual processing (Biederman et al., 1996; Campbell & von Stauffenberg, 2009; Kalff et al., 2002; Wåhlstedt et al., 2008). These findings indicate that both lower and higher order neurocognitive functions measured in young childhood, predict ADHD diagnosis or symptoms a few years later over and above ADHD symptoms at baseline. This is of clinical relevance, since neurocognitive weaknesses in young children are thus a risk factor in the development of ADHD diagnosis or symptoms. There is one point of importance. Studies predicting future ADHD were all performed in very young childhood, thus although neurocognitive functions are risk factors for ADHD diagnosis or symptoms, these studies were not informative in terms of ADHD persistence or remittance.

Since ADHD persisters and remitters could not be differentiated based on neurocognitive functioning in this review, the question of the actual value of neurocognitive functioning in the development of ADHD remains. Although it is possible that neurocognitive functioning in general acts as an epiphenomenon in ADHD, it has been shown that it is valuable to define neuropsychologically impaired subtypes in ADHD (Durston et al., 2011; Nigg et al., 2005; Sonuga-Barke et al., 2010; van der Meer et al., 2012). These neurocognitive subtypes can add to the broader definition of ADHD at the behavioral level, creating more homogeneous groups that may profit from more specialized and individualized treatment (Nigg et al., 2005). A

related question is whether remitters need to be treated or monitored for apparent neurocognitive problems, because these problems might impact outcomes that may be associated with ADHD, such as substance abuse, social functioning, and school performance (see for example Diamantopoulou, Rydell, Thorell, & Bohlin, 2007; Latimer et al., 2003; Miller & Hinshaw, 2010; Molina & Pelham, 2001). Thus, even though ADHD symptoms may be in remission, neurocognitive deficits may negatively impact on other important outcomes, which were not reviewed in this study.

Limitations and Future Recommendations

This review has some limitations. First, our review is limited by the number of studies available in the literature, especially studies that take into account reward processing and temporal processing. Also, in some domains only one aspect was investigated, as for example only reward delay aversion was assessed in studies on reward processing, or RTV in studies on temporal processing, while the predictive value of differences in sensitivity to different types of incentives (reward versus response cost or differences in reward intensity) or time discrimination or time (re)production is not investigated so far. Second, studies differed widely in study design, group definitions, neurocognitive measures used, age of the subjects, follow-up time between assessments and adjustment for possible confounders. In order to minimize issues with regard to different study designs and group definitions, we aggregated results from a similar study design (type-a, -b, or -c, Figure 2.1) and aggregated definitions across studies used to define persistence and remittance (i.e. full persister, full/partial persister, full remitter and full/partial remitter; Table 2.1). Group definitions in terms of persistence/remittance may have an uncalled effect on our results regarding the predictive value of neurocognitive functioning in relation to ADHD. Two studies used strict definitions of ADHD persistence and ADHD remittance and removed subthreshold cases from their analyses (Bédard et al., 2010; Halperin et al., 2008). Other studies combined strict criteria for ADHD persistence with a loose definition of remittance (not fulfilling full criteria for a DSM diagnosis of ADHD) (Fischer et al., 2005; Hart et al., 1995), or combined loose criteria for ADHD persistence (all subjects with more than three or four symptoms of inattention or hyperactivity/impulsivity) with a more strict definition of remittance (Barkley & Fischer, 2011; Biederman et al., 1996; Biederman, Petty, Ball et al., 2009; Mick et al., 2011). Importantly, differences in persistence and remittance definitions are not a likely explanation of the results in this review, since even the study using the most strict criteria to define ADHD persistence and remittance (Bédard et al., 2010) did not differentiate between these two groups using neurocognitive measures. Third, studies differed in sample selection. Two studies included clinical samples (Hart et al., 1995; Langley et al., 2010), and two studies used samples derived entirely from the general population, with one assessing a large birth cohort (Campbell & von Stauffenberg, 2009) and one investigating a

random sample drawn from a full sample (Berlin et al., 2003). The other studies combined clinical samples (subjects with ADHD) with control subjects or drew a selective subsample from a random population sample, based on some behavioral characteristics. The two studies in our review that used clinical samples reported negative results, that is, these studies did not show predictive value of intellectual functioning for ADHD persistence or ADHD symptom change. Studies using participants from a general population sample were able to differentiate ADHD persisters and remitters from controls based on several neurocognitive functions, indicating that findings might be related to the nature of the sample studied, especially regarding patient/control comparisons.

Differences in treatment between ADHD persisters and ADHD remitters may have an uncalled effect on the results. In this review, five out of eighteen studies investigated if medication use influenced the relation between neurocognitive (dys)functioning and ADHD outcome (Barkley et al., 2011; Biederman et al., 1996; Langley et al., 2010; Mick et al., 2011; Vaughn et al., 2011). None of these studies reported contamination by medication of the neurocognitive results. Also, one study reported that the rate of ADHD symptom decline was independent of medication use (Hart et al., 1995). Since results are similar for studies that that did and did not take into account the possible effects of medication, this suggests that medication effects are not a cofactor in explaining the findings of our review. Future studies should investigate to what extent medication effects may influence the results, to prevent uncalled effects. In addition, it is important to ensure that findings for complex higher order neurocognitive functions may not be explained by more basic functions such as processing speed or alerting attentional demands. Since there were no differences between lower order and higher order neurocognitive functions (neither of them differentiated between ADHD persisters and ADHD remitters), it is not very likely that differences in lower level functions will have influenced results for higher level neurocognitive functions in this review. This is confirmed in the one study that adjusted results for group differences in basic processing speed (Kalff et al., 2005). Future studies should carefully consider neurocognitive measures as they usually tap into more than one domain, and include pure measures of lower level neurocognitive functions to check if differences in these lower level components may explain results for higher order functions. Similarly, there may be differences in the interpretation of dependent variables derived from the neurocognitive tasks. For example, SDRT has not only been interpreted as reaction time variability, but it can also reflect little attentional lapses, or state regulation problems (Tamm et al., 2012). In the case of other interpretations, SDRT may nevertheless be considered as reflecting a more automatically controlled, lower level neurocognitive function. In addition, in future studies, follow-up intervals should be wide enough for predicting future ADHD (persistence), as to make sure that the child may has entered another developmental phase. Further, neurocognitive predictive effects should be separately examined for the three symptom domains of

ADHD, which was done only in a minority of studies incorporated in our review (Berlin et al., 2003; Brocki et al., 2010; Campbell & von Stauffenberg, 2009; Marakovitz & Campbell, 1998; Wåhlstedt et al., 2008). Future studies should ideally include both behavioral and neurocognitive assessments in childhood, adolescence and/or adulthood, as to investigate the additive predictive effect of neurocognitive functioning beyond behavioral functioning over time and different developmental phases. Efforts should be made to use identical measures over time.

Conclusion

Despite the heterogeneity of included studies, it can be concluded that ADHD persistence and ADHD remittance cannot be reliably differentiated based on either higher or lower level neurocognitive functioning: both groups generally show poorer functioning compared to typical controls. Furthermore, higher and lower order neurocognitive functions are comparably predictive for the development of future ADHD symptoms (still in childhood), with some predictive effect over and above baseline ADHD. The apparent disentanglement of the age-related changes in neurocognitive deficits and ADHD symptoms may cautiously suggest that neurocognitive deficits can be best seen as epiphenomena, i.e. related to the same etiological factors as the ADHD symptoms but not directly mediating between etiological factors and phenotype. Nevertheless, neurocognitive functions may still be useful in creating more homogeneous subgroups of children with ADHD with distinct prognoses and treatment benefits (Nigg et al., 2005). Better designed studies (longitudinal studies following children from early childhood into adult age, measuring cognition, ADHD and other relevant indicators, thereby also targeting neglected domains such as reward processing, temporal processing, basic information processing speed), are needed to firmly support our conclusions.

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CHAPTER 3

A Six-year Follow-up of a Large European Cohort of Children with ADHD: Outcomes in Late Adolescence and Young Adulthood

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Abstract

Background. There are very few studies on the long-term outcome of children and adolescents with ADHD combined type in Europe. The objective of the present study is to assess the six-year outcome (including pharmacological treatment) of a large cohort of participants with ADHD-combined type (*N*=347, mean age 11.4 years) in late adolescence and early adulthood.

Methods. At study entry and follow-up (mean age 17.4 years), participants were comprehensively assessed on ADHD and comorbid disorders by structured psychiatric interviews and multi-informant questionnaires. Overall functioning was assessed by the Children's Global Assessment Scale. The retention rate was 75.6%.

Results. The majority of participants (86.5%) persisted in a DSM-5 ADHD diagnosis, 8.4% had a subthreshold diagnosis, and 5.1% remitted from the disorder at follow-up. Comorbidities decreased strongly; oppositional defiant disorder: 58% >31%, conduct disorder: 19%>7%. At follow-up, mood- and anxiety disorders were virtually non-existent following strict criteria (1-3%). Percentage of children having had pharmacological treatment at any time increased from 79% to 91%. On the Children's Global Assessment Scale, 48.5% of participants were still functionally impaired at follow-up. Parental ADHD, higher ADHD symptom severity at baseline and higher parent-reported impairment at baseline positively predicted current ADHD symptom severity (R^2=20.9%). Younger baseline age, higher ADHD symptom severity at baseline and higher parent-reported impairment at baseline were positively associated with poorer overall functioning (R^2=17.8%). Pharmacological treatment had no (beneficial) impact on either ADHD symptom severity or overall functioning.

Conclusion. Results confirm that ADHD is largely persistent into late adolescence with severity and family history for the disorder as important risk factors.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention and/or hyperactivity/impulsivity that lead to functional impairments in multiple domains (American Psychiatric Association, 2000). Twenty longitudinal studies show an average childhood ADHD persistence rate of ~15% at age 25 years, although rates in individual studies vary greatly (4-70%) (Faraone, Biederman, & Mick, 2006). These variable findings may be explained by differences in DSM versions used to diagnose ADHD, ADHD subtypes/severity, presence of comorbid disorders, ages at study entry and follow-up, adult ADHD definitions, and whether functional impairment was taken into account. A highly consistent finding is that hyperactive/impulsive symptoms decrease over time, and inattentive symptoms remain relatively stable (Biederman, Mick, & Faraone, 2000; Hart, Lahey, Loeber, Applegate, & Frick, 1995). Further, persistent ADHD is associated with major chronic problems in adult life relative to remitted ADHD, illustrated by higher rates of substance use disorders (Klein et al., 2012) and other psychiatric comorbidities (Barbaresi et al., 2013).

As symptoms of ADHD may persist in adulthood and are related to worse outcomes in adult life, it is of great clinical relevance to investigate predictors of the course of ADHD. Retrospective studies in large representative population samples report that more family adversities (Lara et al., 2009), greater ADHD severity (Kessler et al., 2005; Lara et al., 2009), presence of comorbidities (Lara et al., 2009), and, counter-intuitively, more treatment (Kessler et al., 2005; Lara et al., 2009) in childhood predict ADHD persistence, with good accuracy (receiver operating characteristic = .76 (Lara et al., 2009)). Longitudinal studies confirm the predictive value of family adversities (Biederman, Faraone, Milberger, Curtis et al., 1996; Langley et al., 2010) and comorbidities (Biederman, Faraone, Milberger, Curtis et al., 1996), and provide some support for the predictive value of ADHD familiality (Biederman, Faraone, Milberger, Curtis et al., 1996; Biederman, Petty, Clarke, Lomedico, & Faraone, 2011). As pharmacological treatment is currently the preferred treatment in ADHD, a very important question is whether continued pharmacological treatment is related to outcomes over time as well.

It is important to note that abovementioned studies were limited in several ways. Most studies investigated the prediction of ADHD persistence using dichotomous outcomes (diagnosis yes/no) (Biederman, Faraone, Milberger, Curtis et al., 1996; Kessler et al., 2005; Lara et al., 2009), as opposed to ADHD symptom severity measures. Such a continuous measure may provide a more fine-grained picture of the disorder, and may be less prone to measurement errors than categorical subtypes of ADHD (Lahey & Willcutt, 2010; Willcutt et al., 2012). Second, ADHD symptom severity might not convey the whole picture. An overall measure of functioning based on social,

psychological, and academic functioning more often directly relate to the wellbeing of participants. It may thus be highly relevant to investigate overall functioning as an outcome measure and so far, longitudinal studies assessing the prediction of overall functioning are scarce (but see Biederman, Faraone, Milberger, Guite, et al., 1996). Further, none of the longitudinal studies considered a full set of predictors together, which is important as predictors may overlap, having consequences for measures of prediction accuracy (e.g. explained variance). In addition, analyses so far yielded very limited sample sizes of remitters (n=9) (Biederman, Faraone, Milberger, Curtis et al., 1996). Another important caveat is that not many studies took pharmacological treatment into account, which may have a significant impact on ADHD outcomes (Faraone & Buitelaar, 2010). Finally, there are very few longitudinal ADHD studies in samples outside the United States. Therefore, in the current study we were able to overcome these issues by predicting ADHD outcomes continuously, assessing both symptom severity and overall functioning in a large European cohort, assessing predictors together, and investigating the impact of continued pharmacological treatment.

An important aspect in studies looking at predictors for ADHD outcome is age. As significant developmental processes (neurobiological, psychological, neurocognitive) of an individual are ongoing from childhood through adolescence into adulthood, with a marked transition period in adolescence (Geier, 2013), predictors of ADHD outcome may be moderated by age. For example, higher ADHD severity may have a larger impact on adolescents compared to younger children, as the environment may be more demanding (e.g. school, jobs). So far, studies have investigated either a narrow age range, or did not specifically investigate effects of age. In the current study, we aimed to investigate children in the full range of childhood and adolescence, with careful consideration of linear and quadratic age-dependent effects.

The main aim of the present six-year follow-up of a large cohort of participants with ADHD-combined type was (1) to investigate outcome, i.e. ADHD persistence rates, comorbidity rates, symptom severity and overall functioning, considering age effects, (2) to investigate baseline predictors of both ADHD symptom severity and overall functioning including demographics, ADHD familiality, ADHD severity, comorbidities and pharmacological treatment, considering age effects, (3) to investigate the impact of continued pharmacological treatment until follow-up within the prediction models of ADHD symptom severity and overall functioning.

Methods

Participants

A sample of 347 participants with ADHD combined-type (ADHD/C) aged 5 to 19 years participated in this study. This sample was based on the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study. Between 2003 and 2006, the IMAGE study recruited families with at least one child with clinically diagnosed ADHD/C and at least one additional sibling regardless of possible ADHD status. Clinical diagnosis of each participant was assessed by health-care professionals from clinical child care centers in The Netherlands. In addition, the diagnosis was confirmed, using an extensive assessment protocol described below. The original sample (N = 459) was contacted and invited for follow-up on average 6.0 years (SD = 0.7) after enrolment; 75.6% (N = 347) was retained successfully.

Selection procedures have been detailed previously (Müller et al., 2011). Briefly, inclusion criteria for the IMAGE study were an age of 5-19 years, Caucasian descent, IQ ≥ 70, no diagnosis of autism, epilepsy, general learning difficulties, brain disorders and known genetic disorders. Parent and teacher questionnaires were used to screen participants: Conners' long version (Conners, Sitarenios, Parker, & Epstein, 1998a) and Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). T-scores ≥ 63 on the Conners DSM-IV ADHD subscales Inattention (L), Hyperactivity/impulsivity (M), and Total symptoms (N), and scores ≥ 90th percentile on the SDQ Hyperactivity subscale were considered clinical. Participants scoring clinically on any of these subscales were administered the Parental Account of Children's Symptoms (PACS), a semi-structured, standardized, investigator-based interview with the parents as informants (Taylor, 1986). See Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant (2007) for the algorithm used to derive each of the 18 ADHD symptoms as defined by Diagnostic and Statistical Manual of mental disorders: (DSM-IV-TR; American Psychiatric Association, 2000). Only participants with a diagnosis of ADHD/C based on the algorithm at baseline were included in the current study. Participants came from 282 different families, 81.6% was male. Mean age at baseline was 11.4 years (SD = 2.8) and mean age at follow-up was 17.4 (SD = 2.8).

Diagnostic, Symptom Severity and Overall Functioning Assessment

At follow-up, participants were screened for ADHD using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS), a semi-structured, standardized, investigator-based interview with the parents as informants, and when children were twelve years or older, also with the child (separately) (Kaufman et al., 1997). Participants with elevated scores on any of

the screen items were administered the full ADHD interview. Additionally, parents completed the Conners' Parent Rating Scale-Revised: Long version (CPRS-R:L; Conners et al., 1998a) and the Conners' Teacher Rating Scale-Revised: Long version (CTRS-R:L; Conners, Sitarenios, Parker, & Epstein, 1998b, applied for participants < 18 years), or the Conners' Adult ADHD Rating Scales-Self-Report: Long Version (CAARS-S:L; Conners, Erhardt, & Sparrow, 1999, applied for participants ≥ 18 years). A diagnostic algorithm was used to establish ADHD status according to DSM-5 criteria, which was similar to the algorithm used at baseline (for full description of diagnostic procedures see von Rhein et al., 2015). ADHD subtypes (combined, inattentive, or hyperactive/impulsive subtype) were established following DSM-5 criteria (American Psychiatric Association, 2013). Comorbidities were assessed using the PACS at baseline and using the K-SADS at follow-up. Classifications in both interviews were established according DSM-IV criteria for Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD). Classifications of DSM-IV anxiety-, mood-, and tic disorders were established in the K-SADS at follow-up.

For both the K-SADS and the PACS, interviewers underwent comprehensive training by a team under the supervision of E. Taylor at the London Institute of Psychiatry (IoP; PACS) or JB at the Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen (K-SADS). If additional interviewers were used, each center was responsible for their training and supervision. Inter-rater agreement for the PACS was 0.88 (range 0.71-1.00) and for the K-SADS 0.94 (ADHD), 0.89 (ODD), and 0.95 (CD) (Müller et al., 2011; von Rhein et al., 2015). The interviewers were trained clinicians (child psychiatrists, psychologists) or trained researchers. Persistence of ADHD was defined as meeting full DSM-5 criteria of ADHD/C at baseline, and meeting full DSM-5 criteria of ADHD regardless of subtype, at follow-up. Subthreshold persistence of ADHD was defined as meeting full criteria of ADHD/C at baseline, and meeting criteria of subthreshold ADHD at follow-up: < 6 symptoms of inattention *and* hyperactivity/impulsivity, but ≥ 4 symptoms of inattention *and/or* hyperactivity/impulsivity at follow-up for children < 18 years. For participants ≥ 18 years, thresholds were five and three symptoms respectively. Remission of ADHD was defined as meeting full criteria of ADHD/C at baseline, and not meeting criteria of (subthreshold) ADHD, any subtype, at follow-up.

To assess dimensional persistence, symptom change scores were calculated by subtracting follow-up raw scores from baseline raw scores on the CPRS-R:L ADHD scales L (Inattention), M (Hyperactivity/impulsivity), and N (Total symptoms) (Conners et al., 1998a). Current ADHD symptom severity, and inattentive and hyperactive/impulsive symptom severity were assessed with the follow-up raw scores on the CPRS-R:L scales N, L and M, respectively. Scores on the Conners' ADHD subscales represent combined measures of the number and severity of symptoms.

To measure current overall functioning, the Global Assessment Scale-score of the K-SADS (K-GAS) was administered at follow-up. After finishing the K-SADS interview, the interviewer rated psychological, social and academic functioning, resulting in an overall measure of the current level of functioning ranging between 1 (worst possible level of functioning) and 9 (best possible level of functioning) (Schorre & Vandvik, 2004).

Predictors and Covariates

All predictor variables were assessed at baseline. Five different classes (underlined) were investigated. Demographic variables: Age, sex, and socio-economic status (SES) were measured. SES was calculated from the average educational levels of the parent(s), with educational levels ranging between 0 (no education) and 11 (university), according to an adapted Hollingshead scale (Hollingshead, 1975) fitting the Dutch educational system. ADHD familiality: ADHD familiality was investigated by measuring the percentage of siblings with ADHD according to the PACS interview (Taylor, 1986), and by establishing current parental ADHD status, based on the K-SADS interview (none versus one/both parent(s) with ADHD). ADHD characteristics: ADHD characteristics included ADHD symptom severity, impairment and age of ADHD onset. Symptom severity was measured by the raw score on scale N (range 0-54) of the CPRS-R:L (Conners et al., 1998a). Impairment was measured using both the parent SDQ (Goodman, 1997) and teacher SDQ (range 0-15) (parent and teacher ratings correlated $r = .18$ and were not combined). Age of onset of ADHD was assessed using the PACS interview (Taylor, 1986). Comorbidities: Comorbid DSM-IV defined ODD (yes/no), CD (yes/no) and a screening of the presence of mood/anxiety symptoms (yes/no) were assessed with the PACS (Brookes et al., 2006). Pharmacological treatment: Cumulative intake of psychostimulants from age of onset until our baseline measurement and from age of onset until follow-up were calculated. Lifetime medication transcripts from pharmacies were available for 87% and covered the lifespan for 31% of participants. In addition, a questionnaire was administered to all participants and parents, which assessed lifetime history of psychostimulant medication. When pharmacy transcripts did not fully cover the self-reported treatment period, medication parameters of the missing period(s) were calculated from the questionnaire data and were added to the measures derived from the pharmacy. To optimally take into account daily dose and duration of pharmacological treatment, cumulative intake was calculated by multiplying the mean daily dose (average dose in milligrams for all exposed days; in line with prescription guidelines [NHS, 2008] and given larger direct effects of dexamphetamine on dopaminergic neurotransmission [Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 1998], dexamphetamine dose was multiplied by 2) with treatment duration corrected for age (treatment duration in

months divided by [age minus the minimum start-age within the sample, i.e., 28 months]; see for further details Schweren et al., 2015).

Two potential covariates were investigated. If the univariate relationship between follow-up interval and outcome measures was significant, follow-up interval was entered as a covariate in all subsequent analyses. In addition, study site was entered as a covariate in the final prediction models.

Procedure

At baseline, families were recruited from clinics and via advertisements. Testing took place at the VU University Amsterdam or at the Donders Institute in Nijmegen. Participants were 48 hours off medication during both baseline and follow-up assessments. All ratings of behavioral functioning pertained the participant's functioning off medication. Families were financially compensated for participating in the study. Informed consent was signed by all participants at both measurements, and parents signed for all children in their family as well. The study was approved by the national ethics committee.

Statistical Analysis

Percentage of missing data was < 5% for ADHD diagnoses, current ADHD symptom severity and overall functioning measures, 19% for parental ADHD status, and between 0-9% for the other predictors. Missing value analysis (expectation maximization) was performed for participants with one or two missing items on CPRS-R:L subscales, using all data reported in this study (scale L: 9 participants, scale M: 18 participants). K-GAS-scores were normalised by applying a Van der Waerden transformation.

For our first research question, ADHD persistence rates, percentage of comorbidities, mean symptom change and overall functioning scores were calculated. It was tested whether symptom severity decreased significantly over time and whether changes in hyperactivity/impulsivity symptom severity over time differed from changes in inattention symptom severity. To optimally correct for the familial dependency in our data, Generalized Estimating Equation analyses (GEE) were used, with an exchangeable correlation structure. Additionally, interaction-effects of symptom change between baseline and follow-up with age/age^2 were tested. For our second research question, an optimal set of predictors for current ADHD symptom severity and overall functioning in participants with ADHD/C was derived in three successive

analysis steps. In step 1, GEE analyses were ran on each of the five classes of predictors separately (see Supplemental Table S1 and Supplemental Table S2, also available online), with current ADHD symptom severity or overall functioning as outcome measure respectively. The mean correlation between all predictors was .09 ($.001 < r < .45$), indicating no collinearity. For all predictors, we tested linear effects with outcome measures, except for age. Literature indicated a possible non-linear (quadratic) relationship for the relation between age and our outcome measures (Hart et al., 1995). In step 2, predictors with a p-value < .15 in step 1 were entered into the final GEE model. Finally, in step 3, a backward selection (variables deleted when $p > .05$) procedure was performed for model optimization. Additionally, to investigate possible moderating effects of age on the models for ADHD symptom severity and overall functioning, interactions between both age (assessed at baseline) and age^2 and significant predictors of outcome were added to the final model. When an interaction-effect with age or age^2 was significant, the finding was further explored by testing the final model in subsamples subdivided based on age at baseline (< 12 years and 12 >= years). Final models were further tested separately for symptom severity of inattention and separately for hyperactivity/impulsivity as outcome measures, to explore whether the model was applicable to both symptom dimensions. Further, as the reliability and validity of the CPRS-R:L is only established for children under 18 years of age, we tested whether results of the final model for current ADHD symptom severity replicated in a subsample of children younger than 18 years. Second, the effect of missing data on the final models for both outcome measures was investigated, testing the final model using only participants with complete data. For our third research question, the first three steps of our GEE model were repeated, except that pharmacological treatment until baseline was replaced by pharmacological treatment until follow-up.

Results

Attrition Analysis

Attrition was investigated by comparing participants successfully followed up (75.6%) with participants lost to follow-up on variables reported in this study available at baseline. No significant group differences were found ($.13 < p < .95$).

Current ADHD-Related Outcomes

Table 3.1 shows the descriptives at baseline and follow-up of ADHD diagnosis, comorbidities, symptom severity and overall functioning. Supplemental Table 3.3

Table 3.1. Characteristics of children with ADHD/C at baseline and follow-up

	Mean	SD
Baseline		
Demographic variables		
Age (*yrs*)	11.41	2.78
Sex *(N* / % male)	283	81.6
SES (average educational level of the parents)	5.39	2.21
ADHD familiality		
ADHD status siblings (% of siblings with ADHD)	63.55	26.01
Parental ADHD status (*N* / % ADHD in one or both parents)	96	34.2
ADHD severity[a]		
CPRS-R:L Total symptom severity (scale N)	35.51	8.57
CPRS-R:L Inattentive symptom severity (scale L)	18.59	4.92
CPRS-R:L Hyperactive/impulsive symptom severity (scale M)	16.92	5.19
SDQ Impairment		
-Parent	12.37	3.91
-Teacher	8.03	3.17
Age of onset first ADHD symptoms (*yrs*)	2.25	1.52
ADHD pharmacological treatment		
Mean daily dose (milligram, unit equivalents)	13.31	12.92
Cumulative intake of psychostimulants	53.20	73.74
Comorbidities		
PACS ODD diagnosis (yes)	184	58.0
PACS CD diagnosis (yes)	60	18.9
PACS screen anxiety/depression (yes)	188	59.3
Follow-up		
Demographic variables		
Age at follow-up (*yrs)*	17.36	2.79

ADHD severity[a]		
CPRS-R:L Total symptom severity (scale N)	23.27	11.38
CPRS-R:L Total symptom severity change score (scale N)	12.24	11.69
CPRS-R:L Inattentive symptom severity (scale L)	13.85	6.55
CPRS-R:L Inattentive symptom severity change score (scale L)	-4.74	6.79
CPRS-R:L Hyperactive/impulsive symptom severity (scale M)	9.42	5.98
CPRS-R:L Hyperactive/impulsive symptom severity change score (scale M)	7.50	6.28
ADHD pharmacological treatment		
Mean daily dose (milligram, unit equivalents)	22.04	15.74
Cumulative intake of psychostimulants	126.00	120.49
Status at follow-up		
Kiddie-Global Assessment Scale at follow-up	6.42	1.14
ADHD persistence (*N* / %)	288	86.5
-ADHD/C (*N* / %)	148	51.4
-ADHD/I (*N* / %)	114	40.6
-ADHD/H (*N* / %)	26	9.0
Subthreshold ADHD (*N* / %)	28	8.4
ADHD remitter (*N* / %)	17	5.1
Comorbidities at Follow-up		
ODD (*N* / %)	103	30.8
CD (*N* / %)	22	6.6
Tic disorder (*N* / %)	7	2.1
Mood disorder (*N* / %)	6	1.8
Anxiety disorder (*N* / %)	8	2.5

ADHD = Attention-deficit/hyperactivity disorder; ADHD/C = Attention-deficit/hyperactivity disorder combined-type; ADHD/H = Attention-deficit/hyperactivity disorder hyperactive/impulsive-type; ADHD/I = Attention-deficit/hyperactivity disorder inattentive-type; CD = Conduct Disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Version; ODD = Oppositional Defiant Disorder; PACS = Parental Account of Children's Symptoms; SDQ = Strengths and Difficulties Questionnaire; SES = socio-economic status.

[a] combined measures of parent/self and teacher report.

shows these characteristics in younger and older children (< 12 years and 12 >= years). Of 459 children with ADHD/C at baseline, 333 children (72.5%) had available information on categorical diagnoses at follow-up; 86.5% of them persisted in a full ADHD diagnosis (51.4 % ADHD/C, 39.6% ADHD inattentive-type (ADHD/I), 9.0% ADHD hyperactive/impulsive-type (ADHD/H)), 8.4% had a subthreshold diagnosis, and 5.1% remitted from the disorder. In younger and older children these rates were comparable ($\chi^2 = 2.871$, $p = .720$). Regarding comorbidities at baseline, ODD was apparent in 58.0% of the participants, CD in 18.9% of the participants. At follow-up, ODD was apparent in 30.8% of the participants, CD in 6.6%, tic disorders (any type) in 2.1%, mood disorders (depression or dysthymia) in 1.8%, and anxiety disorders in 2.5% of the participants. Regarding pharmacological treatment, at baseline, 78.8% of the participants have had pharmacological treatment for their ADHD symptoms at any time, compared to 90.9% of the participants at follow-up. At follow-up, 87.1% of participants used methylphenidate (immediate release) at any time, 65.4% used methylphenidate (extended release), and 6.5% of participants used dexamphetamine.

Total raw ADHD symptom severity on the CPRS-R:L scale N decreased from 35.51 to 23.27 ($p < .001$, mean change = 12.24, $SD = 11.69$). Inattentive raw symptom severity on the CPRS-R:L scale L decreased from 18.59 to 13.85 ($p < .001$, mean change = 4.74, $SD = 6.79$), and hyperactive/impulsive raw symptom severity on the CPRS-R:L scale M decreased from 16.92 to 9.42 ($p < .001$, mean change = 7.50, $SD = 6.28$). The decrease in hyperactivity/impulsivity was larger than the decrease in inattention ($p < .001$). Interaction-effects of symptom change between baseline and follow-up with age/age^2 were significant for inattention ($b = .42/.02$ and $p = .003/.004$ respectively), showing that inattentive symptoms decreased more in older than younger children, then leveling off around the age of 16-18 (age at follow-up).

Of 332 participants with current K-GAS-scores available, 161 participants (48.5%) were functionally impaired at follow-up (K-GAS-score ≤ 6). Eight participants (2.4%) had optimal functioning scores (K-GAS-score = 9). Of 288 participants with persistent ADHD and current K-GAS scores available, 153 participants (53.1%) were functionally impaired at follow-up. Two participants (0.7%) with persistent ADHD had optimal functioning scores. Older age was associated with better overall functioning, as reflected in a higher current K-GAS-score ($b = .09$, $p < .001$).

Prediction of Current ADHD Symptom Severity and Overall Functioning

Given our high ADHD persistence rates, prediction models were tested only for our dimensional measures of ADHD. Table 3.2 shows the final prediction models for current ADHD symptom severity. Higher current ADHD symptom severity was

predicted by positive parental ADHD status, higher baseline ADHD symptom severity, and higher parent-reported baseline impairment, explaining 20.9% of variance.

Table 3.2. Final prediction model for current ADHD symptom severity in children with ADHD/C

	B	*b*[a]	*SE*	*p*
Parental ADHD status	0.15	3.53	1.24	.004
CPRS-R:L symptom severity	0.26	0.35	0.08	<.001
SDQ parent-reported impairment	0.25	0.74	0.19	.003
		R^2 = 20.89%		

ADHD = Attention-deficit/hyperactivity disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Version; SDQ = Strengths and Difficulties Questionnaire.
[a] Unstandardized regression coefficient.

Table 3.3 shows the final prediction model for current overall functioning. Lower K-GAS-scores were predicted by younger age at baseline, higher baseline ADHD symptom severity, and higher parent-reported baseline impairment, explaining 17.8% of variance.

Table 3.3. Final prediction model for the current Global Assessment Scale in children with ADHD/C

	B	*b*[a]	*SE*	*p* [b]
Age at baseline	0.15	0.05	0.02	.008
CPRS-R:L symptom severity	-0.26	-0.02	0.004	<.001
SDQ parent-reported impairment	-0.15	-0.04	0.01	.004
		R^2 = 17.75%		

ADHD = Attention-deficit/hyperactivity disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Version; SDQ = Strengths and Difficulties Questionnaire.
[a] Unstandardized regression coefficient. [b] Models are corrected for follow-up interval.

For current ADHD symptom severity none of the predictors interacted significantly with age or age^2 ($.12 < p < .58$). For current overall functioning, there was a significant interaction between age and parent-reported impairment ($p = .029$). Further exploration showed that parent-reported impairment was a significant predictor of current overall functioning only in the subsample of younger participants ($p < .001$) and not in the subsample of older participants ($p = .64$). The prediction model for current ADHD symptom severity (including parental status of ADHD, baseline

symptom severity, and baseline parent-reported impairment) remained significant ($.000 < p < .027$) when tested for ADHD inattention symptom severity ($R^2 = 14.7\%$) and ADHD hyperactivity/impulsivity symptom severity ($R^2 = 20.2\%$).

All predictors in the final model for current ADHD symptom severity remained significant with similar relationships when tested in a subsample with children younger than 18 years ($.002 < p < .010$, $R^2 = 16.9\%$), demonstrating that the findings were not the result of applying the CPRS-R:L in children of 18-24 years old. Findings for current ADHD symptom severity replicated when cases without complete data were removed from the analyses ($.001 < p < .012$, $R^2 = 21.4\%$). Predictors in the final model for current overall functioning remained significant (baseline symptom severity) or marginally significant (age, baseline parent-reported impairment; $.001 < p < .069$, $R^2 = 16.8\%$).

Continued Pharmacological Treatment

To investigate whether continued pharmacological treatment is related to better outcomes (hypothesis 3), pharmacological treatment until follow-up was added to the model predicting current ADHD symptom severity and overall functioning. In the first model, one additional predictors was now significant; more continued pharmacological treatment also predicted higher symptom severity ($b = .011$, $p = .020$). The total model explained 22.5% of variance. For overall functioning, continued pharmacological treatment until follow-up did not contribute to the model.

Covariates

Follow-up interval was significantly related to the K-GAS-score ($b = -0.25$, $p = .001$), but not to ADHD symptom severity ($b = 1.64$, $p = .22$), and therefore was added to the model of overall functioning as a covariate for all subsequent analyses. Further, study site was a non-significant predictor in both the final model of ADHD symptom severity ($b = .22$, $p = .87$) and of overall functioning ($b = .10$, $p = .31$). Adding this covariate to these final models did neither change direction of effects of predictors, nor their significance ($p < .05$).

Discussion

The current European prospective study investigated the course of ADHD/C from childhood to into late adolescence/young adulthood and studied a full set of potential

important predictors for ADHD outcomes: current symptom severity and overall functioning. Importantly, the additional value of continued pharmacological treatment was examined. In summary, although symptom severity decreased, persistence rates were indisputably high: the vast majority of participants had a persistent DSM-5 ADHD diagnosis (86.5%), independent of age. The greater part of ADHD persisters still met combined-type criteria (51.4%). About half (48.5%) of participants were still functionally impaired at follow-up (Kaufman et al., 1997). At follow-up, comorbidity rates (ODD, CD) decreased strongly compared with the baseline measurement. Mood - and anxiety disorders were virtually non-existent following strict criteria (1-3%). The large majority of participants (> 90%) had taken stimulants at some point in time. Predictive variables together explained up to 20% of variance in our outcome measures: higher ADHD symptom severity and higher parent-reported impairment predicted higher current ADHD symptom severity and lower overall functioning. Positive parental ADHD status contributed to the prediction of higher current ADHD symptom severity, while being younger at initial participation predicted lower overall functioning. Age further was important as a moderator in the prediction of overall functioning: parent-reported impairment was predictive only in younger children (< 12 years). Continued pharmacological treatment was of no relevance for overall functioning at follow-up, and against our expectation, pharmacological treatment was positively related to symptom severity at follow-up.

As noted above, ADHD symptom severity decreased significantly, but symptom decrease was only slight, and many adolescents and young adults still fulfilled criteria for a DSM-classification. Although this prospect was expected for the younger part of our sample, a striking finding is that persistence rates were similarly high in the older part of the sample (age up to 25). An important explanation may be our stringent inclusion criteria applied at baseline: ADHD-combined criteria had to be met by all participants, a subtype that was found highly predictive of a persistent course (Lara et al., 2009). Adolescents still meeting full criteria for ADHD/C may be considered as relatively more severely affected compared to younger children meeting these criteria. This may have resulted in one of the highest reported persistence rates thus far; even higher than the 70% persistence rate that was found in the Langley study (2010). The rate of mood and anxiety disorders at follow-up in our sample is lower compared to most other studies (Biederman, Newcorn, & Sprich, 1991). It is possible that participants with higher rates of mood or anxiety disorders were less willing to participate at follow-up. However, there were no differences in comorbidity measures at baseline between participants successfully followed-up or participants lost to follow-up, making this suggestion less likely. Possibly, comorbid problems in ADHD emerge early in childhood and may remit during adolescence, which is what our findings regarding the decrease of ODD and CD rates suggest. For mood disorders, this idea was supported by a study of Biederman and colleagues, showing that comorbid rates of mood disorders in participants with ADHD in adulthood seem comparable to those

in a control group, regardless of higher levels of mood disorders earlier in life in participants with ADHD (Biederman, Petty, Woodworth et al., 2012). For both mood and anxiety disorders, another explanation may (also) hold true. Comparing our results with similar studies that used strict DSM-IV criteria with both parents and participants as informants, an important difference is that we considered a disorder present when it was apparent at the time of assessment, while other studies used wider time-intervals, for example considering a disorder present when apparent within the past three to five years (Biederman, Faraone, Milberger, Curtis et al., 1996; Biederman, Petty, Woodworth et al., 2012).

Our study clearly confirms that ADHD/C is a strongly pervasive disorder at least until adolescence/young adulthood. The relative stability of ADHD symptoms is especially important given that the adolescent brain develops strongly during the transition from puberty into adulthood, marked by increased reward seeking activities leading to problematic decision-making processes (Geier, 2013). In combination with ongoing symptoms of ADHD, this may have unfavorable effects on academic, health, and social outcomes, and may lead to adverse outcomes such as offending behavior. On the other hand, offering a more positive perspective, comorbidity rates decreased strongly and about half of our sample was not severely impaired but had a moderate level of overall functioning.

Current symptoms and overall functioning were predicted by a few variables only, which together explained up to 20% of variance. Not surprisingly, having many symptoms and being highly impaired at baseline predict worse future outcomes, which was also reported by other (Biederman, Faraone, Milberger, Curtis et al., 1996; Molina et al., 2009) but not all studies (Biederman et al., 2011). The positive predictive value of parental ADHD for current symptom severity is consistent with studies showing that broader concepts as 'family history of ADHD' or 'parental psychopathology' are related to ADHD outcomes (Biederman, Faraone, Milberger, Curtis et al., 1996; Langley et al., 2010). This finding may be attributed to genetic factors, but it is also possible that this predictive effect relates to family-environmental factors. As we have shown, parental status of ADHD is a more important predictor than having siblings with ADHD. Given that siblings and parents share a comparable genetic make-up with the proband, and siblings usually have less influence on upbringing than their parents, our finding may indicate an important role for family-environmental factors in the course of ADHD. Finally, younger age at baseline predicted lower overall functioning as well as higher ADHD severity, but the latter only in combination with continued pharmacological treatment. An explanation for this finding is that the world is expanding more for older children compared to younger children. The impact of symptom severity may be relatively smaller then, or may add positively to overall functioning as risk taking behavior may increase, which can be interesting for peers on that age.

Interestingly, our prediction models for ADHD outcomes were largely independent of the developmental phase of participants, confirming the stability of our predictors in a sample of children with ADHD/C with a large age range. Only for current overall functioning parent-reported impairment was a significant predictor in younger children, which may be explained by the smaller involvement of parents when children grow older, with a decrease in correct judgement of impairment levels of their child accordingly.

Cumulative intake of psychostimulant medication neither at baseline nor at follow-up had a beneficial impact on ADHD outcomes or overall functioning in our sample. Moreover, higher cumulative intake at follow-up predicted worse outcomes in terms of ADHD severity. Although ADHD symptoms have been shown to decrease with stimulant treatment, our findings do not support long-term positive effects on outcome. Three other studies also found that ADHD treatment (any type) positively predicted ADHD persistence (Biederman, Petty, O'Connor, Hyder, & Faraone, 2012; Kessler et al., 2005), or ADHD severity (Langley et al., 2010), which was interpreted as treatment being a proxy of ADHD severity. This explanation may also underlie our current finding. In line with this, the results of the Multimodal Treatment study of ADHD (MTA), a large randomized controlled trial comparing the effects of systematic pharmacological treatment, behavioral therapy, a combination of these two, or usual community care, suggested that initial benefits of pharmacological treatment on cognitive functioning and symptom severity dissipated from two years on (Molina et al., 2009). Accordingly, a recent study showed that when psychostimulant medication intake increased in a population of children with ADHD, there were no positive effects on functional outcome measures such as academic outcomes or schooling attainment (Currie, Stabile, & Jones, 2014). Conversely, evidence for negative effects on mood and non-serious adverse events (e.g. sleeping problems, decreased appetite) were evident (Currie et al., 2014; Storebo et al., 2015), indicating that, in line with our findings, the long-term effects of pharmacological treatment on functional outcomes of ADHD may need reconsideration (van de Loo-Neus, Rommelse, & Buitelaar, 2011).

Although we were able to explain a moderate amount of variance in current symptom severity and overall functioning, many of the baseline predictor variables were unrelated to outcomes including sex, SES, pre- and perinatal variables, age of onset, and comorbidities. As we investigated sets of predictors together, it may be that comorbidities were not included in the model as they may overlap with ADHD symptom severity measures. Indeed, ODD was related to ADHD symptom severity in the separate class analyses but did not retain in the model with other predictor variables. Two other studies showed a somewhat larger role for the predictive value of CD (Barkley, Fischer, Smallish, & Fletcher, 2006; Biederman, Faraone, Milberger, Curtis et al., 1996). The first study showed that comorbid CD at baseline was significantly more often seen in ADHD persisters or late remitters (after the age of 12

years) compared to participants that remitted from the disorder before the age of 12 years (Biederman, Faraone, Milberger, Curtis et al., 1996). In the second study, childhood CD as a comorbid condition predicted failure to graduate and young parenthood compared to ADHD childhood CD (Barkley et al., 2006). The discrepancies between these two studies and our findings regarding the predictive value of comorbid CD may be explained by a variety of factors: e.g. the use of different definitions or operationalization of dependent and outcome measures, including different samples or using a different statistical or methodological approach. Further, one study showed that comorbidities were predictive of persistence when using a combined measure (Lara et al., 2009), indicating that a measure of 'general vulnerability' for developing persisting disorders may be of importance. For the other non-significant predictors, our findings are in line with the current literature (Biederman, Faraone, Milberger, Curtis et al., 1996; Biederman et al., 2011; Kessler et al., 2005; Lara et al., 2009).

Limitations and Future Recommendations

Although we studied a relatively large sample of participants with ADHD/C compared to other studies, the sample may have been relatively small for our analyses including interaction-effects with age. Second, including participants with other types of ADHD (such as ADHD/I) would have allowed us to investigate whether these subtypes showed higher remittance rates than ADHD/C. Further, participants were all of Caucasian origin, limiting generalisation to a broader ethnic population. Fourth, interviewers were not systematically blinded for diagnostic status when administering diagnostic interviews. However, since both families and interviewers had no specific interest in the outcome measures in our study, we don't consider this a major bias in the results. Fifth, different diagnostic interviews were used at baseline (PACS) and at follow-up (K-SADS). As both interviews systematically investigated similar DSM criteria for ADHD, we don't expect this difference to have a major impact on our results. Finally, our study was restricted to children with a clinical diagnosis, whereas some previous studies recruited participants with ADHD symptoms from the general population (Barbaresi et al., 2013; Rasmussen & Gillberg, 2000) who may be less severely affected, resulting in higher remission rates. Also, it should be of note that persistence rates may decrease more with older age in adulthood (Barbaresi et al., 2013).

As the majority of variance in ADHD outcomes remain unexplained, far more studies are warranted for a more accurate prediction of future ADHD outcomes. For example, studies should include other variables that relate to family-environmental factors, such as upbringing style or attachment style. Perhaps multiple domains can be integrated in one model, by also including genetic variations, structural and functional brain measures, and neurocognitive factors (Cherkasova, Sulla, Dalena, Ponde, &

Hechtman, 2013; Cortese et al., 2013; Franke et al., 2012; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013).

Conclusion

Our study demonstrates that combined type ADHD strongly persists into late adolescence and young adulthood, posing a challenge for adolescence and adult mental health care as problems do not disappear. Risk factors for worse outcomes in adolescence or young adulthood include high ADHD symptom severity and impairment, younger age, parental ADHD, and more continued pharmacological treatment. The developmental phase of participants was of little importance for our predictors for ADHD outcome, showing the importance of these predictors for the entire ADHD sample. In an era in which pharmacological treatment is the preferred type of intervention, our finding that pharmacological treatment had no positive predictive value for ADHD-related outcomes is clinically important and substantiates further study into this topic. Finally, it is of great relevance for future work to discover the factors that cover the 80% unexplained variance of our models that predict future outcome, to give direction to develop newer and potentially more effective interventions.

Table 3.1 Supplement. Pre-selection of predictors for current ADHD symptom severity

	b^b	*SE*	p^c
Class 1: Demographic variables			
Age (*yrs*)	-0.50	0.23	**.026**
Sex (male=0, female=1)	-3.13	1.77	**.078**
SES (average educational level of the parents)	-0.33	0.28	.238
Class 2: ADHD familiality			
ADHD status siblings (% of siblings with ADHD)	-0.03	0.03	.381
Parental ADHD status (ADHD in one or both parents)	4.91	1.57	**.002**
Class 3: ADHD characteristics			
CPRS-R:L symptom severity (scale N)	0.32	0.07	**<.001**
SDQ parent-reported impairment	0.81	0.17	**<.001**
SDQ teacher-reported impairment	-0.31	0.21	**.134**
Age of onset first ADHD symptoms (*yrs*)	-0.16	0.34	.637
Class 4: Comorbidities			
PACS ODD diagnosis (yes)	3.54	1.36	**.009**
PACS CD diagnosis (yes)	2.32	1.68	.168
PACS screen anxiety/depression (yes)	-0.30	1.31	.819
Class 5: Pharmacological treatment			
Cumulative intake (average daily dose*duration treatment)	0.011	0.01	**.122**

Note: Variables in bold are pre-selected based on a p-value < .15. Predictors were assessed at baseline. ADHD = Attention-Deficit/Hyperactivity Disorder; CD = Conduct Disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Version; ODD = Oppositional Defiant Disorder; PACS = Parental Account of Children's Symptoms; SDQ = Strengths and Difficulties Questionnaire; SES = socio-economic status.

Table 3.2 Supplement. Pre-selection of predictors for current overall functioning

	b[b]	*SE*	*p*[c]
Class 1: Demographic variables			
Age (*yrs*)	0.07	0.02	**.001**
Sex (male=0, female=1)	0.14	0.15	.348
SES (average educational level of the parents)	0.03	0.02	.236
Class 2: ADHD familiality			
ADHD status siblings (%of siblings with ADHD)	-0.002	0.002	.538
Parental ADHD status (yes, ADHD in one or both parents)	-0.30	0.13	**.017**
Class 3: ADHD characteristics			
CPRS-R:L symptom level (scale N)	-0.02	0.004	**<.001**
SDQ parent-reported impairment	-0.03	0.01	**.008**
SDQ parent-reported impairment	-0.02	0.01	.295
Age of onset first ADHD symptoms (*yrs*)	0.01	0.03	.679
Class 4: Comorbidities			
PACS ODD diagnosis (yes)	-0.07	0.11	.530
PACS CD diagnosis (yes)	-0.27	0.15	**.066**
PACS screen anxiety/depression (yes)	-0.18	0.11	**.100**
Class 5: Pharmacological treatment			
Cumulative intake (average daily dose*duration treatment)	0.00	.0001	**.738**

Note: Variables in bold are pre-selected based on a p-value < .15. Predictors were assessed at baseline. ADHD = Attention-Deficit/Hyperactivity Disorder; CD = Conduct Disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised Long Version; ODD = Oppositional Defiant Disorder; PACS = Parental Account of Children's Symptoms; SDQ = Strengths and Difficulties Questionnaire; SES = socio-economic status.

Table 3.3 Supplement. Characteristics of younger and older children with ADHD/C

	Younger < 12 years		Older 12 ≥ years	
	Mean	SD	Mean	SD
Baseline				
Demographic variables				
Age (*yrs*)	9.62	1.70	14.19	1.52
Sex (*N* / %, male)	167	80.3	102	83.6
SES (average educational level of the parents)	5.16	2.11	5.73	2.33
ADHD familiality				
ADHD status siblings (% of siblings with ADHD)	65.25	26.22	60.00	25.04
Parental ADHD status (*N* / % ADHD in one or both parents)	63	36.8	26	26.5
ADHD severity[a]				
CPRS-R:L Total symptom severity (scale N)	35.92	8.29	34.82	9.01
SDQ Impairment				
-Parent	12.50	3.81	11.98	3.95
-Teacher	8.33	3.10	7.38	3.31
Age of onset first ADHD symptoms (*yrs*)	2.29	1.15	2.16	1.51
ADHD pharmacological treatment				
Mean daily dose (milligram, unit equivalents)	11.77	11.43	15.80	14.74
Cumulative intake of psychostimulants	47.01	67.62	63.14	82.00
Comorbidities				
PACS ODD diagnosis (yes)	103	54.2	69	61.6
PACS CD diagnosis (yes)	31	16.3	23	20.5
PACS screen anxiety/depression (yes)	117	61.6	62	55.4

Follow-up				
Demographic variables				
Age at follow-up (*yrs)*	15.63	1.77	20.12	1.67
ADHD severity[a]				
CPRS-R:L Total symptom severity (scale N)	23.98	11.17	22.06	11.68
CPRS-R:L Total symptom severity change score (scale N)	11.93	11.51	12.76	12.03
ADHD pharmacological treatment				
Mean daily dose (milligram, unit equivalents)	23.17	15.67	20.21	15.76
Cumulative intake of psychostimulants	140.76	126.34	102.11	106.57
Status at follow-up				
Kiddie-Global Assessment Scale at follow-up	6.30	1.18	6.61	1.03
ADHD persistence (*N* / %)	178	86.4	110	86.6
-ADHD/C (*N* / %)	88	43.8	51	43.6
-ADHD/I (*N* / %)	73	36.3	38	32.5
-ADHD/H (*N* / %)	13	6.5	13	11.1
Subthreshold ADHD (*N* / %)	17	8.3	11	8.7
ADHD remitter (*N* / %)	11	5.3	6	4.7
Comorbidities				
ODD (*N* / %)	65	31.4	38	29.7
CD (*N* / %)	14	6.8	8	6.3
Tic disorder (*N* / %)	5	2.4	2	1.6
Mood disorder (*N* / %)	3	1.5	3	2.4
Anxiety disorder (*N* / %)	4	2.0	4	3.2

ADHD = Attention-Deficit/Hyperactivity Disorder; ADHD/C = Attention-Deficit/Hyperactivity Disorder combined-type; ADHD/H = Attention-Deficit/Hyperactivity Disorder hyperactive/impulsive-type; ADHD/I = Attention-Deficit/Hyperactivity Disorder inattentive-type; CD = Conduct Disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long Version; ODD = Oppositional Defiant Disorder; PACS = Parental Account of Children's Symptoms; SDQ = Strengths and Difficulties Questionnaire; SES = socio-economic status.

[a] combined measures of parent/self and teacher report.

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4

CHAPTER 4

Neurocognitive Predictors of ADHD Outcome: A Six-year Follow-up Study

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Abstract

Background. Although a broad array of neurocognitive dysfunctions are associated with ADHD, it is unknown whether these dysfunctions play a role in the course of ADHD symptoms.

Methods. The present longitudinal study investigated whether neurocognitive functions assessed at study-entry (mean age = 11.5 years, *SD* = 2.7) predicted ADHD symptom severity and overall functioning 6 years later (mean age = 17.4 years, 82.6% = male) in a carefully phenotyped large sample of 226 Caucasian participants from 182 families diagnosed with ADHD-combined type. Outcome measures were dimensional measures of ADHD symptom severity and the Kiddie-Global Assessment Scale (K-GAS) for overall functioning. Predictors were derived from component scores for 8 domains of neurocognitive functioning: working memory, motor inhibition, cognitive inhibition, reaction time variability, timing, information processing speed, motor control, intelligence. Effects of age, gender, and pharmacological treatment were considered.

Results. Results showed that better working memory predicted lower ADHD symptom severity (R^2 = 3.0%), and less reaction time variability predicted better overall functioning (higher K-GAS-score, R^2 = 5.6%). Predictors were still significant with baseline behavior included in the models.

Conclusion. The role of neurocognitive functioning in the long term outcome of ADHD behavior is discussed.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common developmental disorder, with impairing and highly persistent symptoms of inattention and/or hyperactivity/impulsivity (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011). Impairment exists in several domains of functioning, including academic, social, and occupation functioning (Barkley, Fischer, Smallish, & Fletcher, 2006). Patients with persistent ADHD experience chronic problems in adult life compared to those with remitted ADHD, such as higher rates of substance use disorders (Klein et al., 2012) and other psychiatric comorbidities (Barbaresi et al., 2013). It is important to elucidate factors involved in the course of ADHD, since 'baseline' predictors that would allow prediction of the course of ADHD in terms of ADHD symptom severity and overall functioning could be used to inform parents and children. Such information may also guide further study into treatment; for example investigating whether neurocognitive training of a particular predictive function might enhance prognosis.

Neurocognitive functioning may act as predictor of symptom severity and overall functioning of ADHD, as neurocognitive dysfunction is a key aspect of the disorder (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008) and is at the heart of several models of ADHD (Barkley, 1997; Sergeant, 2000; Sonuga-Barke, Bitsakou, & Thompson, 2010). The relevance of neurocognitive functioning for the course of ADHD has been emphasized by Halperin and Schulz (2006). According to their model, higher-order mental functions (so-called cognitive control functions as inhibition and working memory) may contribute to better outcome.

To evaluate the hypothesis that neurocognitive functioning may act as a predictor for ADHD outcome, we recently reviewed existing literature. Some of the studies showed positive associations between concurrently assessed neurocognitive performance and ADHD outcome in adolescents (Barkley & Fischer, 2011; Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014; Halperin, Trampush, Miller, Marks, & Newcorn, 2008). However, as baseline measures of neurocognitive performance were not available in most of these studies, it remains unknown whether the associations were apparent earlier in childhood yet. On the basis of six studies that investigated the predictive value of early assessed neurocognitive functions, we concluded that ADHD symptom remission was not predicted by neurocognitive functioning (van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). This conclusion was largely supported by more recent studies. One study showed that only one out of nine neurocognitive functions (attentional set-shifting) predicted greater decrease in ADHD symptoms 10 years later (Coghill et al., 2014). In addition, recent work has shown that neurocognitive functions in childhood were not related to ADHD outcome in adolescence (McAuley, Crosbie, Charach, & Schachar, 2014), and that neurocognitive functions in 3-to-4 year olds were not related to changes in ADHD severity 4.5 years

later (Rajendran, Trampush, et al., 2013). One study showed that an aggregated measure of neurocognitive functioning was related to ADHD severity 1 year later in children between 5-7 years but not in children between 4-5 years: better functioning predicted lower ADHD severity (Rajendran, Rindskopf, et al., 2013). Finally, in one study that assessed ADHD symptoms, two out of four neurocognitive measures (working memory and reaction time variability) in preschool predicted future symptoms of inattention (Sjöwall, Bohlin, Rydell, & Thorell, 2015). Taken together, there is only little evidence to predict ADHD outcomes based on early neurocognitive functions.

However, these findings may be related to limitations of the available literature. The first limitation is related to the type of outcome measure chosen. Available studies have focused mainly on dichotomous outcomes (diagnosis yes/no), rather than on more sensitive continuous measures of symptom severity (Lahey & Willcutt, 2010; Willcutt et al., 2012). Also, some studies exclusively focused on ADHD core symptoms and did not assess accompanying levels of impairment. Outcome as measured in terms of the level of overall functioning may clinically be more relevant. The second limitation relates to the type of neurocognitive assessment used. Only few studies were conducted on key neurocognitive functions associated with ADHD, such as cognitive control, temporal processing and reward processing (van Lieshout et al., 2013). Also, most of the longitudinal studies did not consider a full set of neurocognitive predictors together, which is important as predictors may overlap. Focusing on one domain also narrows clinical applicability. In addition, not many studies investigated whether early neurocognitive functions predict outcomes over and above ADHD behavior, which is of importance to rule out the possibility that neurocognitive functions act simply as a proxy for ADHD severity. Fifth, most studies have not investigated developmental and gender effects. Regarding developmental effects, it is thought that development of an individual is ongoing from childhood into adulthood with a sharp transition period in adolescence (Geier, 2013). Also, neurocognitive development is likely to be non-linear (Vaughn et al., 2011). Therefore, it is important to consider moderating effects of age when investigating outcomes over time. Previous studies so far investigated a narrow age range or did not specifically investigate possible moderating effects of age. For example, only in very young children (3 to 6 years), neurocognitive functioning predicted ADHD status or severity several years later (Rajendran, Rindskopf, et al., 2013; van Lieshout et al., 2013). Also, it is possible that gender might impact on results, given differences in brain structure and function in healthy controls (Bell, Willson, Wilman, Dave, & Silverstone, 2006), and that prevalence rates of ADHD are higher in males than in females (Willcutt, 2012). Finally, few studies took effects of pharmacological treatment into account. This may be of importance, as pharmacological treatment may impact on outcomes; for example, in a meta-analysis including 23 studies, it was found that both amphetamine and

methylphenidate products were efficacious in treating ADHD symptoms (Faraone & Buitelaar, 2010).

The current study addressed the abovementioned issues by employing a dimensional approach to investigate the predictive value of neurocognitive functioning for (1) ADHD symptom severity and (2) overall functioning, using a longitudinal design with a 6-year follow-up of children with combined-type ADHD (ADHD/C). We investigated children in the full range of childhood age, with careful consideration of age-dependent effects. As ADHD is associated with heterogeneity in neurocognitive deficits (Nigg, Wilcutt, Doyle, & Sonuga-Barke, 2005), we assessed a broad array of neurocognitive functions to capture as much as possible this heterogeneity. We used measures of cognitive control (motor inhibition, cognitive inhibition, working memory) and temporal processing (variability in responding, timing), as well as other functions that show impairments in individuals with ADHD (basic information processing speed, motor control, and intellectual functioning). In addition, neurocognitive performance may differ between subtypes (Dovis, van der Oord, Huizenga, Wiers, & Prins, 2015). Therefore, including only participants with ADHD/C and not participants with the inattentive or hyperactive/impulsive subtype, might increase homogeneity in neurocognitive functioning as well. The predictive value of neurocognitive functions for ADHD symptom severity and overall functioning was studied taking into account baseline symptom severity and impairment as well, respectively. Age, gender, pharmacological treatment and study site were additionally considered as confounding variables. Taking into account limitations of earlier studies, we tested the hypotheses that better early neurocognitive functioning would be associated with lower symptom severity and better overall functioning at follow-up. As the available literature did not allow us to form specific hypotheses, we expected similar results for ADHD symptom severity and overall functioning (i.e., better neurocognitive functioning related to better outcomes: lower symptom severity and better overall functioning), since overall functioning is highly dependent on the expression and consequences of the primary symptoms (Caci et al., 2015).

Methods

Participants

Participants (N = 459) with a DSM-IV-TR diagnosis of ADHD/C aged 5-19 years were recruited from outpatient clinics and via advertisements between 2003 and 2006 in the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study. Six years later, subjects were invited for a comprehensive follow-up assessment as part of the NeuroIMAGE study (von Rhein et al., 2015). The period between baseline and follow-up assessment was on average 6.0 years (SD = 0.7) and 347 participants (75.6%)

were retained successfully. Of these 347 participants, 226 participants participated in the neuropsychological assessment during the IMAGE study (baseline measurement) and were included in the current study. Results of attrition analyses are described in the Results section.

Selection and diagnostic procedures at baseline have been detailed previously (Müller et al., 2011a, 2011b). Briefly, inclusion criteria for entry at baseline were an age of 5-19 years, Caucasian descent, IQ ≥ 70, no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, and known genetic disorders, and having at least one sibling (regardless of ADHD status). The parent and teacher Conners' long version (Conners, Sitarenios, Parker, & Epstein,1998) and Strengths and Difficulties Questionnaire (SDQ; Goodman 1997) were used to screen participants: *T*-scores ≥ 63 on the Conners' ADHD subscales L (DSM-IV Inattentive symptoms), M (DSM-IV Hyperactive/impulsive symptoms), and N (DSM-IV Total symptoms), and scores ≥ 90th percentile on the SDQ Hyperactivity subscale were considered clinical. Participants obtaining clinical scores on any of these subscales were administered the Parental Account of Children's Symptoms (PACS), a semi-structured, standardized, investigator-based interview with the parents as informants (Taylor, 1986). See Rommelse, Oosterlaan, Buitelaar, Faraone, and Sergeant (2007) for the algorithm used to derive each of the 18 ADHD symptoms as defined by the DSM-IV-TR (American Psychiatric Association, 2000). The 226 participants included in the current study with ADHD/C at baseline came from 182 different families. Their mean age at baseline was 11.5 years (*SD* = 2.7), and 17.4 years (*SD* = 2.7) at follow-up, and 82.6% was male. Regarding medication use at follow-up, 88.5% of all participants used stimulants, 11.9% of all participants used atomoxetine, 4.9% of all participants used antidepressants, and 1.3% of all participants used tranquillizers (e.g., benzodiazepines, anxiolytics).

Outcome measures. At follow-up, ADHD total symptom severity as well as inattentive and hyperactive/impulsive symptom severity were assessed with the Conners' Parent Rating Scale–Revised: Long version (CPRS-R:L; Conners et al., 1998) scales N (DSM-IV Total symptoms; Cronbach's α = .93), L (DSM-IV Inattentive symptoms; Cronbach's α = .90) and M (DSM-IV Hyperactive/impulsive symptoms; Cronbach's α = .87), respectively. Scores on the Conners' ADHD subscales represent combined measures of the number (maximum 18) and severity (range 0-3) of symptoms, with scores ranging between 0 and 54 (maximum number of symptoms; 18, with maximum severity; 3), or between 0 and 27 (maximum number of symptoms within one symptoms axis; 9, with maximum severity; 3), respectively. Raw scores were used.

The Global Assessment Scale-score (K-GAS) of the Dutch version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime

Version (K-SADS; Kaufman et al., 1997) administered at follow-up to both the parent and the child ≥ 12 years separately, was used to measure overall functioning. This measure is a time-efficient and clinically relevant measure of overall functioning. After finishing the K-SADS interview, the interviewer rated psychological, academic and social functioning. This resulted in an overall measure of the current level of functioning ranging between 1 (worst possible level of functioning) and 9 (best possible level of functioning; Schorre & Vandvik, 2004).

For both the K-SADS and the PACS, interviewers of the participating centers underwent comprehensive training by a team under the supervision of E. Taylor at the London Institute of Psychiatry (PACS) or JB at the Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen (K-SADS). Trained interviewers used the same training and supervision procedures for additional interviewers at the participating centers. Inter-rater agreement for the PACS was .88 (range .71-1.00; Müller et al., 2011a) and for the K-SADS .94 (ADHD), .89 (ODD), and .95 (CD; von Rhein et al., 2015). The interviewers were trained clinicians (child psychiatrists, psychologists) or trained researchers.

Predictor variables. We investigated eight domains of neurocognitive functioning measured at baseline: working memory, motor inhibition (the ability to stop a prepotent response), cognitive inhibition (the ability to flexibly shift between two response options), reaction time variability, timing, information processing speed, motor control, and intelligence. Domains were chosen to include a broad array of neurocognitive tasks (see Table 4.1) that are known to be sensitive to detect differences between children with ADHD and control children (Rommelse, Altink, Martin, et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008), and that yield enough variance in order to be useful as predictors of differences in symptom severity and overall functioning (Nigg et al., 2005). For each neurocognitive domain, we performed a principal component analysis (PCA) to optimize the number of predictor variables and reduce error variance; a total of eight principal component analyses thus were performed. First, we selected the most widely used and theoretically valid independent measures for each domain, thereby including at least two measures in each PCA with the exception of the domain of intelligence, for which only one measure (based on four subtests) was available. When two measures from one task within a domain correlated > .85, one of the measures was excluded from the PCA to prevent clustering of highly correlated variables.

Table 4.2 provides a description of the neurocognitive domains and corresponding measures that were finally included in our principal component analyses, with descriptive information and the principal component score per measure. For working memory, we initially included four measures. Of these four measures, 'number of identified targets' (NIT) and 'number of identified targets in the correct order' (NITco)

Table 4.1. Description of instruments

Task	Measure	Description	References
WISC/WAIS-III Digit Span	- Maximum Span Forwards - Maximum Span Backwards	An auditory task to measure the accuracy of verbal working memory; a sequence of numbers was announced, and should be replicated forwards (or backwards in the backwards condition), with increasing length.	Wechsler 2000, 2002.
ANT Visuo-Spatial Sequencing Task	- Total number of identified targets in correct order	A computerized task to measure the accuracy of visuo-spatial working memory; a sequence of circles in a 3x3 grid should be replicated in the correct order by pointing to them, with increasing length.	Rommelse et al. 2008(a) De Sonneville 1999
Stop Task	- RT on go-trials (ms) - SDRT on go-trials (ms), corrected for MRT. - Stop Signal Reaction Time (ms) - Percentage commission errors	A computerized task to measure the speed and accuracy of inhibition of an ongoing response; go-trials required an accurate response to an external cue, with two choices (left or right); stop-trials required no response to an external cue.	Rommelse et al. 2008(a) Logan and Cowan 1984
ANT Shifting Attentional Set	- RT Block 1 (ms) - SDRT Block 1, corrected for MRT	Block 1: A computerized task to measure the speed and variability of motor output in response to an external cue, with two choices (left or right).	Rommelse et al. 2007a De Sonneville 1999
	- RT Block 2 (ms), corrected for MRT Block 1 - Percentage errors, corrected for errors Block 1	Block 2: As in block 1, but in block 2 an *incompatible* response was required (pressing a button in the direction opposite to which the stimulus moved).	
ANT Baseline Speed	- RT (ms) - SDRT, corrected for MRT.	A computerized task to measure the speed and variability of motor output in response to an external cue, (simple reaction time task)	Rommelse et al. 2008b De Sonneville 1999
Motor Timing Task	- SDRT, corrected for MRT (ms) - Mean absolute deviation (ms)	A computerized task to measure the accuracy and variability of motor timing, requiring a response on a button when a subject thought a 1second interval had elapsed after a tone.	Rommelse et al. 2008b Van Meel et al. 2005

Time Test	- Percentage of deviation visual modality (mean of three highest intervals) - Percentage of deviation auditory modality (mean of tree highest intervals)	A computerized task to measure the precision of the reproduction of five time intervals (4, 8, 12, 16, 20sec); A light bulb (visual modality) or a tone (auditory modality) was presented for a specific interval length, which had to be reproduced thereafter.	Rommelse et al. 2007b Barkley, 1998
ANT Pursuit	- Absolute deviation left hand	A computerized task to measure the precision of motor control; a randomly moving target should be followed as precisely as possible by moving a mouse cursor.	Rommelse et al. 2007c De Sonneville 1999
ANT Tracking	- Absolute deviation left hand	A computerized task to measure the precision of motor control; an invisible midline should be traced with a mouse cursor as quickly and precisely as possible, between an inner and an outer circle.	Rommelse et al. 2007c De Sonneville 1999
WISC/WAIS-III Vocabulary, Similarities, Block Design, Picture Completion	- Estimated total IQ	Four subtests of the WISC/WAIS were used to estimate full-scale IQ.	Wechsler 2000, 2002.

ANT = Amsterdamse Neuropsychologische Taken; MRT = Mean reaction time; RT = Reaction time; SDRT = Standard deviation of reaction time; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler Intelligence Scale for Children

Table 4.2. Description of principal components

Neurocognitive domain	Task	Dependent variables	*M*	*SD*	Range (min-max)	Component scores
Working memory	ANT visuo-spatial sequencing task	Total number of identified targets in correct order	87.81	12.20	39.0-105.0	.42
	WISC/WAIS-III Digit Span	Maximum span forwards	5.21	1.10	3.0-9.0	.41
		Maximum span backwards	3.81	1.12	2.0-7.0	.45
Motor inhibition	Stoptask	SSRT	293.87	90.60	100.0-608.1	.54
		Percentage commission errors	3.64	3.54	0.0-15.1	.54
Cognitive inhibition	ANT shifting attentional set, block 2	Reaction time (corrected[b]) (ms)	230.84	174.11	-243.7-871.4	.63
		Percentage errors (corrected[b])	8.86	12.55	-15.0-50.0	.63
Reaction time variability	ANT baseline speed	SDRT (corrected[a], ms)	0.40	0.24	0.14-1.2	.24
	ANT shifting attentional set, block 1	SDRT (corrected[a], ms)	0.37	0.18	0.10-1.0	.41
	Stop task	SDRT go trials (corrected[a], ms)	0.23	0.04	0.13-0.35	.41
	Motor timing	SDRT (corrected[a], ms)	0.28	0.09	0.07-0.58	.43
Timing	Motor timing	Mean absolute deviation (ms)	273.50	146.90	49.9-741.7	.38
	Time test, visual modality	Percentage of deviation	21.34	13.76	2.4-63.6	.39
	Time test auditory modality	Percentage of deviation	24.19	14.62	4.1-69.3	.39
Information processing speed	ANT baseline speed	Reaction time (ms)	360.11	81.38	224.0-638.0	.42
	ANT shifting attentional set, block 1	Reaction time (ms)	269.08	920.50	269.1-920.5	.41
	Stoptask	Reaction time go trials (ms)	591.41	114.48	357.8-1051.1	.36
Motor control	ANT Pursuit	Absolute deviation left hand	5.90	2.98	2.0-15.0	.58
	ANT Tracking	Absolute deviation left hand	2.85	1.83	0.5-8.4	.58
Intelligence	WISC/WAIS-III Vocabulary, Similarities, Block Design, Picture Completion	Total IQ	99.46	11.68	70.0-133.0	-

ANT = Amsterdamse Neuropsychologische Taken; PCA = Principal Component Analysis; SDRT = Standard Deviation of Reaction Time; SSRT = Stop Signal Reaction Time; WISC = Wechsler Intelligence Scale Children; WAIS-III = Wechsler Adult Intelligence Scale-third edition.

[a] Corrected for mean reaction time. [b] Corrected for reaction time or errors in block 1.

correlated >.85 with each other. Therefore, we decided to discard NIT from the PCA, because NITco not only captures increasing length (load), but also captures correct order, hence offering a more valid measure of working memory (Baddeley, 2012). For motor control, we initially included the mean absolute deviation and the standard deviation of the mean distance of two motor control measures (Pursuit and Tracking). However, both measures of the standard deviation correlated >.85 with the mean absolute deviation on the corresponding task. As the mean absolute deviation on the task is the most widely used measure of motor control, we decided to discard the standard deviations of both tasks from the PCA. The PCA was conducted using a correlation matrix, calculated on standardized data. Results showed one component with an Eigenvalue > 1 (cut-off value) for each domain. Principal components were rescaled so that higher scores represent better performance. For reaction time variability, smaller variability was interpreted as better performance. See Table 4.3 for a description of group means and standard deviations of the predictor and outcome variables. Supplemental Table 4.1 (also available online) provides correlations between baseline/follow-up behavioral variables (symptom severity, overall functioning and impairment) and neurocognitive predictors.

Covariates. As there is a strong relationship between baseline behavior and behavior at follow-up, models predicting symptom severity were calculated with and without baseline ADHD symptom severity (CPRS-R:L scale N: DSM-IV Total symptoms; Cronbach's α=.85). Likewise, baseline impairment was included when predicting overall functioning. Impairment at baseline was measured by the impairment scale of the Strengths and Difficulties Questionnaires (SDQ; Cronbach's α=.75; Goodman, 1997), reported by parents (range 0-21). When follow-up interval was significantly related to current symptom severity, follow-up interval was included as a covariate in further analyses. Follow-up interval was defined as the time between baseline and follow-up measurement (in years). The same procedure was followed when overall functioning was predicted. Age and age^2 (assessed at baseline), gender, pharmacological treatment until follow-up and study site (Amsterdam or Nijmegen) were added as covariates to the final models. Pharmacological treatment was collected in terms of the cumulative intake of psychostimulants (mean daily dose multiplied with treatment duration corrected for age) from age of onset until the follow-up assessment using information from pharmacy records supplemented with information from parent questionnaires. See van Lieshout et al. (2016) for further details.

Table 4.3. Descriptives of predictor and outcome variables

	M	min	max	*SD*
Baseline Variables				
Working Memory	0.0001	-3.90	4.47	1.37
Motor Inhibition	-0.001	-4.77	2.24	1.29
Cognitive Inhibition	0.006	-4.09	2.16	1.11
Reaction time variability	-0.003	-4.37	2.73	1.32
Timing	-0.008	-5.21	2.03	1.51
Information Processing Speed	-0.01	-6.25	2.54	1.46
Motor Control	0.01	-4.44	1.68	1.21
Intelligence	99.46	70.00	133.00	11.68
CPRS-R:L Inattentive symptom severity (scale L)	18.55	2.00	27.00	5.07
CPRS-R:L Hyperactive/impulsive symptom severity (scale M)	16.73	2.00	27.00	5.39
CPRS-R:L Total symptom severity (scale N)	35.29	6.00	52.00	8.99
SDQ Impairment (parent)	11.98	0.00	21.0	3.91
Follow-up Variables				
CPRS-R:L Inattentive symptom severity (scale L)	14.09	0.00	27.00	6.38
CPRS-R:L Hyperactive/impulsive symptom severity (scale M)	9.26	0.00	27.00	5.80
CPRS-R:L Total symptom severity (scale N)	23.32	0.00	52.00	11.01
K-GAS-Score	6.49	2.00	9.00	1.08
Follow-up Interval	5.85	4.40	7.68	0.65
Pharmacological treatment (cumulative intake of stimulants)	118.27	0.00	477.44	111.88

Note: Scores of neurocognitive measures are component scores. ADHD = Attention-Deficit/Hyperactivity Disorder; CPRS = Conners' Parent Rating Scale-Revised: Long version; K-GAS = Kiddie-Global Assessment Score; SDQ = Strengths and Difficulties Questionnaire; PC = Principal Component.

Procedure

Testing at baseline and follow-up took place at the VU University Amsterdam, or at the Donders Institute for Brain, Cognition and Behaviour, Radboud University in Nijmegen, the Netherlands. Participants were 48 hours off medication before both baseline and follow-up assessments. All ratings of behavioral functioning pertained the participant's functioning off medication. Families were financially compensated for participation. Informed consent was signed by all participants at both measurements, and parents signed for all children in their family as well. The study was approved by the national and local ethics committees.

Statistical Analysis

In the sample of 226 children, the Stop task was not administered to 9.7% of participants due to technical problems. Between 0.4-3.1% of data were missing for other neurocognitive predictors. Missing value analysis (Expectation Maximization with 25 iterations) for Stop Task data was performed only for participants with at

least nine out of ten neurocognitive tasks available (n = 22). Percentage of missing data at follow-up was 2.2% for ADHD symptom severity measures, and 3.1% for overall functioning measures. All outcome variables had a normal distribution with values of skewness and kurtosis within the range of -1 to +1, except for the K-GAS score (kurtosis = -1.20). K-GAS-scores were normalized by applying a Van der Waerden transformation.

To optimally correct for the familial dependency in our data, Generalized Estimating Equation analyses (GEE) were used with an exchangeable correlation structure. An optimal set of predictors for (1) symptom severity and (2) overall functioning was derived by performing a backward selection procedure (variables deleted when $p >$ .05), until an optimal final model was composed. The mean correlation between predictors was .36 (.03 $\leq r \leq$. 70), indicating no collinearity. Analyses predicting symptom severity or impairment used three steps: (1) Models predicting symptom severity or impairment were calculated with the neurocognitive predictors only (model 1). (2) To investigate the additional predictive value of neurocognitive functioning over and above baseline behavior or baseline impairment, models were calculated with the neurocognitive predictors together with baseline symptom severity or baseline impairment (model 2). (3) Then, models were calculated with baseline symptom severity or baseline impairment only, for comparison (model 3). We described differences between the models (1) and (2), by evaluating the difference in R^2.

Additional analyses. To investigate age effects, both age and quadratic effects of age were examined. Interactions between age and significant predictors of outcome were added to the final models with neurocognitive functioning (model 1). When an interaction-effect with age or age^2 was significant, the finding was further explored by testing the final model in subsamples subdivided based on age at baseline (<12 years and 12 >= years). The same procedure was followed for gender. The final model of ADHD symptom severity (model 1) was reran using both inattentive and hyperactive/impulsive symptoms as outcome measures (including baseline symptom severity), to explore whether the model was applicable to both symptom axes.

Sensitivity analyses. As the reliability and validity of the CPRS-R:L is only established for children under 18 years of age, we checked whether results of the final model for ADHD symptom severity (model 1) were robust when tested in children younger than 18 years. Beside possible moderating effects of age and gender, we tested possible effects of confounders (age, age^2, gender, pharmacological treatment, study site) on the final models.

Results

Attrition Analyses

Attrition was investigated by comparing participants successfully followed up (i.e., included in our analyses, $N = 226$) with participants lost to follow-up from the total sample on 25 variables available at baseline (age, gender, ADHD symptoms, neurocognitive measures). Participants who were lost to follow-up had higher SD (corrected for MRT) on the motor timing task ($p < .001$) and had more commission errors on the Stop task ($p = .036$). No other significant group differences were found ($.070 < p < .983$).

Prediction of ADHD Symptom Severity

Follow-up interval was not related to current ADHD symptom severity ($p = .675$). Table 4.4 shows the final prediction model. Better working memory predicted lower ADHD symptom severity, explaining 3.0% of variance. When taking baseline symptom severity into account, better working memory still predicted lower ADHD symptom severity, together explaining 11.7% of variance. For comparison, baseline symptom severity alone explained 10.0% of variance.

Table 4.4. Final prediction models for current ADHD symptom severity in children with ADHD/C

	b	*SE*	*p*
Model 1			
Working memory	-1.34	0.45	.003
	R^2 = 3.00%		
Model 2			
Working memory	-1.05	0.51	.041
CPRS-R:L symptom severity	0.43	0.06	<.001
	R^2 = 11.71%		

Note: *b* is the unstandardized coefficient. ADHD = Attention-Deficit/Hyperactivity Disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long version.

Prediction of Overall Functioning

Follow-up interval was related to the K-GAS-score ($b = -0.29$, $p < .001$) and therefore included as a covariate in all further analyses. Table 5 shows the final prediction model. Higher reaction time variability predicted lower K-GAS-scores, explaining 5.6% of variance. When taking baseline parent-reported impairment into account,

higher reaction time variability still predicted lower K-GAS-scores, together explaining 8.6% of variance. For comparison, baseline parent-reported impairment alone explained 7.1% of variance.

Table 4.5. Final prediction models for current overall functioning in children with ADHD/C

	b	*SE*	*p*
Model 1[a]			
Reaction time variability	0.11	0.05	.018
	R^2 = 5.60%		
Model 2[a]			
Reaction time variability	0.10	0.04	.030
SDQ impairment parent	-0.04	0.01	.003
	R^2 = 8.62%		

Note: *b* is the unstandardized coefficient. ADHD = Attention-deficit/hyperactivity disorder; SDQ = Strengths and Difficulties Questionnaire.
[a] Models are adjusted for follow-up interval.

Additional Analyses

Age and gender effects. Significant neurocognitive predictors for both ADHD symptom severity (working memory) and overall functioning (reaction time variability) did not significantly interact with age (b = 0.02, p = .882/b = 0.01, p = .499 respectively), age^2 (b < 0.001, p = .978 / b < 0.001, p = .621 respectively), or gender (b = -1.09, p = .411 / b = -0.13, p = .231, respectively).

Effects of Predictors on Inattention and Hyperactivity/Impulsivity. Working memory (model 1) was not a significant predictor for ADHD inattention symptom severity (p = .174), but was a significant predictor for current ADHD hyperactivity/impulsivity symptom severity; better working memory predicted lower hyperactivity/impulsivity symptom severity (p = .001). R^2 for the final model of hyperactivity/impulsivity was 3.91%.

Sensitivity Analyses

Sample < 18 years. Predictors relevant in the final model (model 1) for current ADHD symptom severity were significant with similar relationships when tested in a subsample of children younger than 18 years (b subsample= -1.43 / ß = -0.15, p = .040, R^2 = 1.6%, versus b full sample = -1.34 / ß = -0.17; p = .003, R^2 = 3.0%). Taking into

account that the sample size of this subsample was substantially smaller, these findings suggest that the results also hold when the age group was excluded for which the CPRS-R:L was not validated.

Covariates. Findings for current ADHD symptom severity as well as for overall functioning replicated when age or age^2, gender, pharmacological treatment, or study site were added as covariates to the final models (model 1). Covariates were not significant in the final models for ADHD symptom severity and overall functioning ($.068 < p < .830$).

Discussion

The current large prospective study investigated whether a broad array of well-defined neurocognitive measures predicted dimensional outcome measures of ADHD, 6 years later, in children and adolescents with ADHD-combined type. In summary, better working memory predicted lower symptom severity 6 years later, and less reaction time variability predicted better overall functioning. Percentage of explained variance for the neurocognitive predictors was small (3.0-5.6%) but significant. Together with baseline behavior, neurocognitive predictors remained significant, and a higher percentage of variance was explained compared to the percentage of variance explained by the baseline behavioral measures or neurocognitive measures alone.

The current finding that both better working memory and less reaction time variability contribute to better outcomes is in line with our hypothesis that better early neurocognitive functioning is associated with a positive outcome of ADHD. Interestingly, our finding is also consistent with the results of a recent study in which ADHD symptoms were assessed on a continuum both at baseline and follow-up, showing that better working memory and less reaction time variability predicted future ADHD symptoms and academic achievement, over and above baseline behavioral symptoms (Sjöwall et al., 2015). Notably, also other studies suggested that impairments in working memory and larger reaction time variability are most prominent of all neurocognitive functions involved in ADHD (Castellanos & Tannock, 2002; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Tamm et al., 2012). Previous studies, however, did not find predictive value of both verbal and spatial working memory for future ADHD status or symptoms (Biederman et al., 2009; Coghill et al., 2014). These discrepant findings may relate to differences between other studies and our study; e.g., smaller sample size (Biederman et al., 2009; Coghill et al., 2014), using dichotomous outcome measures compared to continuous measures (Biederman et al., 2009), and longer lengths of follow-up interval (Biederman et al., 2009). Also, previous studies measured the domain-specific aspects of phonological loop or visuo-

spatial sketchpath (e.g., digit span or arithmetic subtests of the WISC/WAIS [Biederman et al., 2009] or visuospatial working memory in a forward form [Coghill et al., 2014]). In our study, we used a component measure of verbal (both a forward and backward condition) and visuospatial working memory. Possibly, with such a measure, we investigated a more domain-general central executive aspect of working memory (Kofler et al., 2014), which may have greater predictive power and may explain discrepancies in findings from other studies. By using different measures and tasks of working memory, we also tried to avoid a general issue regarding working memory, namely the debate about the exact underlying neurocognitive function that is assessed with span tasks (Aben, Stapert, & Blokland, 2012; Cowan, 2008; Davelaar, 2013). Our finding that better working memory specifically predicted lower hyperactivity/impulsivity symptom severity, is in line with one study showing that the performance in the domain-general central executive aspect of working memory was significantly related to children's activity level, which suggests that hyperactivity may act as a compensatory mechanism for working memory (Rapport et al., 2009). Regarding reaction time variability, to our knowledge, no other study investigated this neurocognitive function as predictor for future ADHD symptom severity or overall functioning.

Surprisingly, early inhibitory functioning and timing abilities did not predict current symptom severity or overall functioning. These results contrast the view that these functions act as core deficit in ADHD (Barkley, 1997; Durston, van Belle, & de Zeeuw, 2011; Toplak, Dockstader, & Tannock, 2006). Furthermore, these results are inconsistent with previous studies in our sample showing large deficits within the domain of inhibitory functioning and timing (Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008; Rommelse, Altink, Oosterlaan, Beem, et al., 2008; Rommelse, Oosterlaan, et al., 2007). However, earlier studies confirm that inhibitory functioning and timing abilities may not predict ADHD outcomes (McAuley et al., 2014; van Lieshout et al., 2013). Our data suggest that relations between neurocognitive functioning and ADHD outcomes over time may differ between neurocognitive functions that are thought to be closely related.

There are some alternative explanations that should be discussed in relation to our findings. The finding that many of our baseline neurocognitive measures did not predict future outcomes, gives rise to the thought that the development of neurocognitive performance may not relate to ADHD outcomes at all, which would theoretically be of interest. In addition, it is possible that neurocognitive functioning and overall functioning are not even related to each other at baseline (such as ADHD and neurocognitive functioning), which would explain that we did not find a longitudinal relationship between most of our neurocognitive measures and overall functioning in particular.

In this study, we addressed questions regarding age, gender, pharmacological treatment, follow-up interval and study site, to contribute to existing literature. Previous studies revealed mainly negative findings on the predictive value of early neurocognitive functions for ADHD outcomes. As brain development is thought to be non-linear (Giedd et al., 1999), with, for example, a developmental spurt in adolescence (Casey, Jones, & Somerville, 2011), we expected moderating effects of age on the relation between relevant neurocognitive predictors and ADHD outcomes. Surprisingly, our models were independent of age. Similarly, predictive effects were independent of gender. According to our findings, relations between both working memory and response variability and ADHD outcomes were not confounded by the duration of medication taken until follow-up. Moreover the duration of medication taken had no beneficial effect on our ADHD outcomes, as medication use was a non-significant predictor in the models. This finding is consistent with findings of the MTA study showing that over 6 to 8 years, there was no advantage of pharmacological treatment on ADHD outcomes (Molina et al., 2009). Long-term benefits on academic and occupational outcomes, social functioning and comorbidities are also questionable (Langberg & Becker, 2012; van de Loo-Neus, Rommelse, & Buitelaar, 2011). Pharmacological treatment is one of the preferred treatments in ADHD and may have adverse side effects as well. Our results and previous findings failing to support long term benefits of pharmacological treatment stress the importance of more work in this important area of research. Another issue is that follow-up interval was related to a lower K-GAS-score. Further exploring this relationship showed us that younger children were the ones with longer follow-up intervals; it may thus well be possible that this finding reflects the larger impact ADHD has on the overall functioning of younger children. Study site was not a factor of relevance to our data.

Taken together, the predictive value of neurocognitive functioning for ADHD outcomes is small; smaller than we expected based on the well-established and moderate to strong relationship between ADHD behavior and neurocognitive functioning observed cross-sectionally. The small relationship between baseline neurocognitive functioning and behavioral outcomes on the long term that we found, together with earlier findings on this topic (Coghill et al., 2014; McAuley et al., 2014; Rajendran, Trampush, et al., 2013; van Lieshout et al., 2013) shows that neurocognitive functioning may not be seen as protective or a risk factor for longer term behavioral outcomes. These findings clearly indicate that further research is needed to understand the role or neurocognitive functioning in ADHD, for example by setting up longitudinal studies that look into more complex interactions of neurocognitive functioning with genetics and environment (e.g., family environment, peer group influences) and look at more than symptom outcome and functioning such as social behavior and self-esteem (Savitz, van der Merwe, Stein, Solms, & Ramesar, 2007). Based on our findings, it may be suggested that working memory and variability in responding are the promising neurocognitive measures that can contribute to such multimodal prediction models.

Clinically, our findings indicate that although working memory and variability in reaction time are independently predictive of ADHD outcomes, these effects are of such small magnitude that our findings are yet of little relevance for reliably establishing prognosis. This means that we are not able to predict which children with ADHD will improve on their level of behavioral symptoms and/or impairment based on their neurocognitive performance at an earlier time point. Our findings do not rule out the possibility that neurocognitive profiling to establish current strengths and weaknesses still may be of relevance for improving and supporting (school/occupational) functioning at the current moment, or to help understand and explain certain behavioral problems or impairments.

Some limitations should be noted. First, some aspects of our sample limit generalization to the population, including our exclusive focus on participants with the combined type of ADHD (Lara et al., 2009), the limited representation of girls in our sample and the inclusion of Caucasian individuals. Second, we did not verify medication use with the participant, which may have resulted in a less than optimal estimation of medication use in reality. Third, although we did include a broad array of neurocognitive functions, we were not able to include all neurocognitive domains currently regarded important in ADHD, such as reward related neurocognitive functions. Our findings thus cannot be generalized to other neurocognitive domains. Fourth, we have chosen to use performance-based measures of neurocognitive functioning. Rater-based measures of neurocognitive functioning may show higher predictive value, as these measures may be more closely related to behavior and investigate capacities in more unstructured situations, which may better mirror 'real-life' functioning. Fifth, for the investigation of the value of neurocognitive functioning over and above baseline behavior, we used the exact same measures for baseline symptom severity and follow-up symptom severity. This may partly explain the higher percentage of explained variance for baseline symptoms compared to neurocognitive functioning.

To further disentangle the complex relation between neurocognitive functioning and ADHD symptoms, future studies could take into account both neurocognitive functioning at baseline and at follow-up, in order to look at the relation between neurocognitive development over time and the course of ADHD. In addition, a person-based analysis in which neurocognitive profiles within one person are investigated might shed more light on this issue as well. Patterns of neurocognitive performance within one person might be better suited to predict future outcomes such as symptom severity and overall functioning. Such approaches might enable us to further understand the complexity of the development of behavior and understanding mechanisms of recovery from problematic behavior. Adding key concepts in ADHD such as reward processing may add to a more complete understanding of ADHD.

In conclusion, using a broad array of early neurocognitive functions to predict current ADHD symptom severity and overall functioning, we found only little evidence for the hypothesis that a stronger neurocognitive profile (better working memory, smaller reaction time variability) predicts better outcome. Our findings challenge the role of neurocognitive functioning in the long term outcome of ADHD.

Table 4.1. Supplement. Correlations between baseline and follow-up behavioral measures and neurocognitive predictors

		Pearson correlation (*r*)											
		1	2	3	4	5	6	7	8	9	10	11	12
1	Baseline ADHD symptom severity (CPRS-R:L scale N)	-											
2	Follow-up ADHD symptom severity (CPRS-R:L scale N)	**0.32****	-										
3	Baseline impairment (SDQ impairment parent)	**0.44****	**0.36****	-									
4	Follow-up overall functioning (K-GAS-score)	-0.11	**-0.22****	**-0.18****	-								
5	PC working memory	-0.13	**-0.19****	-0.12	**0.15***	-							
6	PC motor inhibition	-0.07	-0.04	0.04	0.11	**0.38****	-						
7	PC cognitive inhibition	-0.04	-0.10	-0.01	0.02	**0.34****	0.07	-					
8	PC reaction time variability	-0.09	-0.10	**-0.15***	**0.14***	**0.55****	**0.53****	**0.18****	-				
9	PC timing	-0.11	-0.07	-0.07	**0.14***	**0.59****	**0.43****	**0.21****	**0.70****	-			
10	PC information processing speed	-0.07	-0.05	-0.06	0.08	**0.60****	**0.37****	**0.36****	**0.64****	**0.57****	-		
11	PC motor control	-0.07	-0.07	-0.07	**0.15***	**0.42****	**0.37****	**0.17***	**0.49****	**0.48****	**0.56****	-	
12	Intelligence (TIQ)	-0.09	-0.05	-0.10	0.06	**0.30****	0.04	**0.17***	**0.23****	**0.24****	**0.16***	0.03	-

ADHD = Attention-deficit/hyperactivity disorder; CPRS = Conners' Parent Rating Scale-Revised: Long version; K-GAS = Kiddie-Global Assessment Score; SDQ = Strengths and Difficulties Questionnaire; PC = Principal Component.

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

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7

CHAPTER 7

Summary and Discussion

Predicting Clinical Outcome in Children with ADHD
Is there a Role for Neurocognitive Functioning?

The aim of the current thesis was to advance our knowledge of the course of Attention-Deficit/Hyperactivity Disorder (ADHD), and the role of neurocognitive functioning in ADHD behavior and overall functioning, using longitudinal information from individuals with ADHD-combined type (ADHD/C), their unaffected siblings and controls. Participants were included from the Dutch part of the International Multicenter ADHD Genetics (IMAGE; baseline) and NeuroIMAGE (follow-up) projects. Specific aspects such as age and pharmacological treatment were taken into account in an attempt to capture the complex relationship between neurocognitive and behavioral functioning using a longitudinal sample. This thesis was written with both a descriptive and a predictive perspective as (a) the course of ADHD symptoms (symptom change and persistence rates), comorbid problems and functional impairment was described, as well as the course of neurocognitive functioning, and (b) ADHD outcomes (ADHD symptom severity and symptom change, overall functioning and comorbid problems) were predicted from behavioral and neurocognitive characteristics using information from baseline and follow-up.

In the next sections, the main results from each chapter of this thesis will be summarized (see also Table 7.1 for an overview). Subsequently, we will discuss the findings on the course of ADHD and its neurocognitive characteristics, to what extent ADHD outcomes can or cannot be predicted, and will try to draw some conclusion regarding specific models in which the course of ADHD and the role of neurocognitive functions were described earlier. In addition, clinical implications will be discussed. This chapter will finish with a discussion of strengths and limitations of the studies of this thesis and future recommendations will be provided.

Summary of the Main Findings

In **chapter 2**, a systematic overview of studies that investigated the predictive value of neurocognitive functioning for prospective ADHD was provided. Relevant studies published between 1990 and 2011 were included. Based on eighteen studies there was no evidence that either automatically controlled (requiring little mental effort; lower level), or more consciously controlled (requiring high levels of mental effort; higher level) neurocognitive functions differentiated ADHD persistence from remittance; overall, both persisters and remitters showed weaker performance than typically developing controls, although the effect was smaller for remitters. Further, neurocognitive functions measured in childhood were able to predict ADHD a few years later, regardless of the type of neurocognitive function. Our findings do not support the model of Halperin and Schulz (2006), which suggests a stronger maturation of more consciously controlled neurocognitive functions in ADHD remitters. Further, several neurocognitive functions seem to be useful to prospectively differentiate individuals with ADHD from controls in childhood.

In the other chapters (**3-6**) in this thesis, we investigated participants from the IMAGE and NeuroIMAGE cohort. In **chapter 3 and 4**, affected siblings (ADHD/C) were included. Additionally, in **chapter 5 and 6,** unaffected siblings and control children were included, thereby covering the full ADHD spectrum from no to severe symptom levels. In **chapter 4-6,** identical neurocognitive measures were investigated (i.e. verbal working memory, temporal processing [including timing and variability], reaction time speed, and motor control). In **chapter 4,** this battery was extended by measures of visuo-spatial working memory, motor and cognitive inhibition. We could not include those particular measures at follow-up, as these measures were adjusted for use in the Magnetic Resonance Imaging (MRI)-scanner at follow-up (visuo-spatial working memory, motor inhibition), or differences between ADHD and control children appeared to be due to differences in baseline task (e.g. speed) differences instead of higher order cognitive functioning (cognitive inhibition). Please see Table 7.1 for details on participant and study characteristics of each chapter.

In **chapter 3**, we investigated the course of ADHD/C from childhood/adolescence into (late) adolescence/young adulthood, and additionally studied a full set of potential predictors for ADHD outcomes over a six-year interval. Although symptom severity decreased, persistence rates were indisputably high: the vast majority of participants had a persistent Diagnostic and Statistical Manual (DSM)-5 diagnosis (86.5%), independent of age. The greater part of ADHD persisters still met combined type criteria (51.4%). Only a very small amount (5.1%) of the participants fully remitted from the disorder. However, since only about half of the sample was functionally impaired at outcome, prognosis is generally rather favorable. Moreover, comorbidity rates (Oppositional Defiant Disorder [ODD], Conduct Disorder [CD]) decreased

strongly over time, and mood- and anxiety disorders were virtually non-existent following strict criteria (1-3%), indicating that overall outcome was better than baseline functioning. The large majority of participants (> 90%) had taken stimulants at some point in time. These findings indicate that although ADHD diagnoses strongly persist, a steady decrease in ADHD and comorbid symptoms is observed and functional impairments attenuate in a substantial proportion. Predictive variables explained up to 20% of variance in our outcome measures: Higher ADHD symptom severity and higher parent-reported impairment prospectively predicted higher ADHD symptom severity and lower overall functioning. A current ADHD diagnosis of (one of) the parent(s) contributed to the prospective prediction of higher ADHD symptom severity, while the child being younger prospectively predicted lower overall functioning. Continued pharmacological treatment had no beneficial impact on ADHD outcomes or overall functioning. In addition, higher cumulative intake of medication until follow-up predicted worse outcomes in terms of ADHD severity, probably explained by a confounding effect where more severe cases had a higher chance of taking medication. Findings on predictors suggest that some variables (e.g. severity, family history for the disorder) may be important risk factors, however, the largest part of variance remains unexplained, needing further investigation.

This was done in **chapters 4-6**, in which the prospective predictive value of neurocognitive functioning (**chapter 4**) and the relationship between longitudinal characteristics of neurocognitive functioning (**chapter 5 and 6**) for ADHD outcomes were investigated. As our review in **chapter 2** showed that studies with a larger follow-up interval (i.e. >3 years) and a broader age range (i.e. age > 12 years) are absent so far, we aimed to fill this gap in **chapter 4**, in which we investigated baseline neurocognitive predictors of ADHD outcomes, using a broad array of neurocognitive measures. These neurocognitive predictors were derived from component scores for eight domains: Working memory, motor inhibition, cognitive inhibition, reaction time variability, timing, information processing speed, motor control, and intelligence. The results revealed that better working memory predicted lower ADHD symptom severity, and less reaction time variability predicted better overall functioning, with a small percentage of explained variance (3-5.6%). Our neurocognitive predictors were significant over and above baseline behavior (e.g. ADHD symptoms), and neurocognitive functions together with ADHD behavior explained a higher percentage of variance compared with models with behavioral or neurocognitive measures alone. The models were independent of age, gender and pharmacological treatment. Finding only few predictive neurocognitive functions with small predictive value challenges the role of neurocognitive functioning in the outcome of ADHD and is in line with findings from chapter 2.

In **chapter 5**, we investigated the neurocognitive course in multiple domains in ADHD affected as well as unaffected siblings and controls, and subsequently tested whether

this course mapped onto dimensional ADHD outcomes at follow-up. It appeared that affected and unaffected siblings trended to, or fully caught up with performance levels of controls at follow-up on four (44.4%) and five (55.6%) of the nine dependent variables, respectively. Within this trending pattern, only measures of time production, motor control, and an overall measure of neurocognitive functioning showed a full catch-up. In contrast, performance in remaining key neurocognitive measures (i.e. verbal working memory, variability in responding, but also intelligence) remained impaired at follow-up. Importantly, in terms of the predictive value, the course of neurocognitive functioning generally was not to related to ADHD outcomes, suggesting that improvement or deterioration of neurocognitive functioning does not translate one-to-one into (ADHD) behavior. Findings indicate not just a maturational delay, but suggest more complex models. Also, the etiological link between neurocognitive deficits and ADHD outcomes in adolescents and young adults is questioned and appear in line with findings of chapter 2 and 4.

As the predictive value of neurocognitive functioning was limited in chapter 2, 4 and 5 with only small effect sizes, in **chapter 6** a novel person-based approach was taken to capture heterogeneity and developmental aspects in ADHD, by identifying homogeneous longitudinally informed neurocognitive subgroups. We then examined whether these homogeneous subgroups would link to ADHD outcomes. This was done in individuals with ADHD/C, their unaffected siblings and controls, using neurocognitive measures at two time points. Latent class analysis (i.e. detecting latent neurocognitive subgroups based on patterns of associations between the included neurocognitive measures) revealed three longitudinally stable, mainly quantitatively different neurocognitive subgroups, one characterized by overall weak (inaccurate slow) performance, another by a fast yet accurate performance and a third group showing an overall average profile. As expected, the inaccurate slow subgroup had the worst clinical outcomes at follow-up, with a higher odds ratio for having an ADHD diagnosis at follow-up (3.10, 95% CI [2.05, 4.69]) and 2.21, 95% CI [1.32, 3.70]) compared to the overall average subgroup and the fast yet accurate subgroup respectively. In terms of clinical applicability of the findings, an overall weak neurocognitive profile is reason for concern, since it is a less common phenomenon in control children, clearly increases the odds for a persistent form of ADHD and may even index a risk for late onset ADHD in children at familial risk for ADHD. In addition, our findings suggest that this overall weak profile is a relatively stable neurocognitive profile with apparently very few children showing relative improvements over time. Including the overall weak profile in clinical practice for ADHD as an indicator could increase the accuracy of prognosis and (very tentatively) may even be useful in early detecting of siblings at risk for developing late-onset forms of the disorder. Future studies are needed to examine this issue in clinical practice.

General Discussion

The Course of ADHD Symptoms and Neurocognitive Functions: A Matter of Delay?

Following the maturational lag hypothesis mentioned in the Introduction section, one would expect that at a certain developmental stage, ADHD symptoms should decrease to the level of typically developing controls. Also, it is suggested that due to maturation, underlying deficits (for example neurocognitive deficits, but note that this statement is also based on another hypothesis, assuming a certain association between neurocognitive functioning and behavior) would remit together with remitting symptoms; development is "just" delayed, not qualitatively different. Our results provide some important insights regarding the question whether ADHD is a matter of maturational delay. One of them is the strong persistence rate of initially combined-type ADHD (86.5%) until young adulthood that we have observed in **chapter 3**. This persistence rate is one of the highest reported thus far; even higher than the 70% persistence rate that was found in the study of Langley and colleagues (2010), which included children with all types of ADHD ≤ 13 years at baseline. This finding contrasts with the hypothesis that with maturation, children with ADHD catch up in their behavior with equal-aged typically developing peers.

An explanation for our high persistence rate may be that we included only children with ADHD/C, a subtype that includes more symptoms to fulfill DSM-criteria compared to the other subtypes. Also, adolescents meeting combined type criteria at baseline may be considered as relatively more severely affected compared to younger children meeting these criteria as these adolescents could have been remitted yet but apparently did not. If the suggestion that the baseline inclusion of only the most ADHD severe subtype may have led to a higher persistence rate is correct, special attention should be drawn to these adolescents with ADHD/C in clinical practice compared to the other subtypes. Being adolescent and still fulfilling criteria of the combined type may indicate a certain risk for persisting behavioral problems. The relative stability of ADHD observed in this thesis is especially important given that the adolescent brain develops strongly during the transition from puberty into adulthood, marked by increased reward seeking activities leading to problematic decision-making processes (Geier, 2013). In combination with ongoing symptoms of ADHD, this may have unfavorable effects on academic, health, and social outcomes, or may lead to adverse outcomes such as offending behavior. Consistent with this view is that more than 50% of the ADHD persisters is still significantly functionally impaired at outcome, indicating that indeed, functioning is importantly compromised still in adolescence and young adulthood. Taken together, our results indicate that in children with combined type ADHD, the course of ADHD symptoms generally is not, or at least not only, understood by a delayed maturation in childhood and adolescence.

While persistence rates are high, ADHD symptoms decreased significantly (**chapter 3**), which is in line with other studies that show that 15% versus 65% remain symptomatic at age 25 depending on the definition of persistence (Faraone, Biederman, & Mick, 2006). Almost 10% of all participants with ADHD/C decreased in symptom levels to the extent that they now fell in the category of subthreshold ADHD, and half of all ADHD persisters attained an inattentive (majority) or a hyperactive/impulsive (minority) subtype diagnosis instead of a combined subtype. This difference in persistence in terms of meeting full DSM-criteria versus persistence in terms of symptom levels evidently illustrates the difference between a continuous and a dichotomous approach, which is consistent with the findings in the earlier mentioned comprehensive meta-analysis (Faraone et al., 2006). It is possible that with further aging, symptoms may further decrease and eventually lead to remittance. However, given the prevalence rates of ADHD in adults (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009) and the high persistence rates and compromised overall functioning that we observed in 50% of participants in young adulthood, remittance perhaps is not cut out for every individual and clearly is not yet set for a large proportion in adolescence and young adulthood. Taken together, looking at the continuous level, a general pattern of decrease in symptom severity is observed which may be in accordance with a maturational delay hypothesis, however, this decrease is so small that an indisputably high number of children remains fulfilling ADHD criteria and compromised overall functioning, suggesting a maturational delay alone is not sufficient to explain these ongoing problems.

Of note, a relevant issue in the discussion on persistence and remittance of ADHD symptoms is to what extent comorbid problems persist over time. In **chapter 3**, we have demonstrated that the rate of comorbidities, in the form of oppositional, conduct, mood and anxiety disorders decreased over time, which is particularly notable compared to most other studies showing higher rates of comorbidities (Biederman, Newcorn, & Sprich, 1991), but is also evident compared to the clearly persisting pattern of ADHD. The course of comorbid problems seems to differ from that of ADHD symptoms, by showing a stronger decrease. This stronger decrease in comorbid problems may suggest that separate mechanisms are involved in the decrease of comorbid problems as opposed to the stronger persistence of ADHD symptoms. Alternatively, a 'U-shape' development may exist, in which ADHD symptoms emerge first, followed by comorbid problems, and with time (or maturation), the comorbid problems remit first, followed by a decrease in ADHD symptomatology. When such a mechanism is at work here, that may indicate that the stronger decrease in comorbid problems in our sample could predict the further decrease of ADHD symptoms in time.

Our results so far do not confirm that a maturational delay in ADHD is apparent in (most) individuals with ADHD/C. In an attempt to further understand pathophysiological mechanisms that may increase our insight into the course of

ADHD, many studies have investigated neurocognitive functions (e.g. Frazier, Demaree, & Youngstrom, 2004; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Pauli-Pott & Becker, 2011; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), some of them also from a longitudinal perspective (e.g. Barkley & Fischer, 2011; Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014; Mick et al., 2011; Rajendran, Rindskopf, et al., 2013; Rajendran, Trampush, et al., 2013; Vaughn et al., 2011), or by studying neurocognitive functions in adults with ADHD (Bálint et al., 2009; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Bridgett & Walker, 2006; Hervey, Epstein, & Curry, 2004; Schoechlin & Engel, 2005). We extended this knowledge in **chapter 5** by investigating the course of a broad range of neurocognitive functions over a six-year follow-up interval, from which one interesting point clearly withstands. The majority of functions in unaffected and affected siblings showed a trending pattern into the direction of normalization (time reproduction, time production variability, reaction time speed) or even fully caught-up with performance levels of controls (time production, motor control, aggregated neurocognitive functioning). Importantly, however, for remaining functions that were suggested key domains in ADHD (e.g. working memory, reaction time variability), the initial gap in performance between (un)affected siblings and controls remained over time. Our findings confirm results reported in other studies regarding patterns of neurocognitive normalization in ADHD for some functions (Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005; McAuley, Crosbie, Charach, & Schachar, 2014; Miller, Loya, & Hinshaw, 2013), while other functions show partial normalization and some functions remained impaired (Hervey et al., 2004; Mostert et al., 2015). No clear pattern emerged regarding the type of functions that did and did not show normalization. For example, we could not clearly differentiate between lower (more automatically controlled) or higher (requiring a high level of effort) order functions or otherwise (Halperin & Schulz, 2006). Nevertheless, we can conclude that findings do not entirely fit the hypothesis of a maturational delay, as three important neurocognitive functions (verbal working memory, variability in responding and intelligence) remained impaired when all participants reached adolescence and young adulthood. This is confirmed by the lack of a significant effect of age on patterns of catch-up, which would have been evident following the maturational lag hypothesis as it assumes that an individual would show a 'growth spurt' leading to normalization at a certain developmental stage. So for both the behavioral as for the neurocognitive data, evidence does not support the suggestion that ADHD is 'only' a matter of delay, at least not for most of the individuals. More complex mechanisms probably are involved in the further course of the disorder, which will be discussed further on.

Predicting ADHD Outcomes: Are Neurocognitive Functions Valuable, Beyond Behavior?

ADHD thus persists in a large majority - at least in individuals with combined-type ADHD - and persistent ADHD is associated with major chronic problems in adult life relative to remitted ADHD (Barbaresi et al., 2013; Klein et al., 2012), indicating the importance to investigate predictors of the course of ADHD or ADHD outcomes. Below we will summarize and discuss our findings regarding behavioral and neurocognitive predictors, as well as demographic variables, familiality and pharmacological treatment.

First, results regarding the prediction of ADHD were quite disappointing as a meaningful longitudinal relationship between predictors (mostly neurocognitive but also some other, see further) and ADHD behavior was largely absent. For example, many of the non-neurocognitive variables (e.g. sex, socio-economic status, age of ADHD onset, and comorbidities) that we included in **chapter 3** were unrelated to ADHD outcomes when investigated together with other significantly predicting factors (e.g. ADHD symptom severity, parent-reported impairment, current parental ADHD status). In addition, based on an extensive search in the literature (**chapter 2**) as well on our results in **chapter 4**, we were not able to detect a generally convincing and clinically meaningful relationship between neurocognitive functioning at one point of time in children and adolescents with ADHD for prospective ADHD symptom severity, ADHD change, or overall functioning. Unfortunately, we were also not able to provide evidence that ADHD outcomes could be predicted based on the course of neurocognitive functioning over and above baseline behavior (**chapter 5**). Moreover, a person-based approach using latent class analyses revealed that three distinct more or less severity based longitudinally informed neurocognitive subgroups all contained a significant amount of controls, unaffected and affected siblings, again indicating that the predictive value of neurocognitive functioning is limited.

Alternatively, a few variables were (mostly to a small extent) related to ADHD outcomes and overall functioning: First, non-neurocognitive characteristics as ADHD severity (more symptoms and greater impairment), parental ADHD status (a current ADHD diagnosis of [one of] the parent[s]) and younger age were positively predictive for worse ADHD outcomes in children with ADHD/C (**chapter 3**). These results were consistent with some (Biederman et al., 1996; Molina et al., 2009) but not all (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011) studies showing the predictive value of symptom severity and overall functioning. In addition, our findings are consistent with studies that found positive predictive value for concepts as family history of ADHD or parental psychopathology (Biederman et al., 1996; Langley et al., 2010). Furthermore, on the positive predictive value of neurocognitive functions, **chapter 2** demonstrated that neurocognitive functions measured in young childhood

are able to predict prospective ADHD compared to control status, still in childhood. In addition, **chapter 4** illustrated that there is predictive value for working memory (composite score of verbal and visual working memory) regarding prospective ADHD symptom severity, and predictive value for reaction time variability regarding prospective overall functioning, both with a small effect, over and above baseline measures. Interestingly, as other studies found working memory and reaction time variability to be the most promising of all neurocognitive functions involved in ADHD (Castellanos & Tannock, 2002; Martinussen et al., 2005; Tamm et al., 2012), observing (little) predictive value precisely for these two neurocognitive functions of ADHD outcomes may indicate that working memory and reaction time variability are indeed most central to ADHD. It is notable that this finding is in line with a recent study in which ADHD symptoms were assessed on a continuum both at baseline and follow-up, showing that better working memory and less reaction time variability predicted prospective ADHD symptoms and academic achievement, over and above baseline symptoms (Sjöwall, Bohlin, Rydell, & Thorell, 2015). So, these findings justify at least further investigation into the predictive role of working memory and reaction time variability in ADHD symptom development. Results from **chapter 6** yielded that detecting longitudinally informed neurocognitive subgroups may be helpful to index a vulnerable group; generally and developmentally stable inaccurate slow neurocognitive performance is related to the worst (ADHD-related) outcomes compared to an overall average performing subgroup and a fast yet accurate subgroup, confirmed by odds ratios of about 2 to 3 for the inaccurate slow versus the fast yet accurate, and overall average subgroup respectively, respectively. Another finding from **chapter 6** cautiously pointed to another link between neurocognitive functioning and ADHD, namely that unaffected siblings in the inaccurate slow subgroup were at higher risk to develop ADHD later on compared to those in the fast yet accurate subgroup.

Taken all findings together, the overall pattern thus was a disappointing absence of predictive value of neurocognitive functioning and some other characteristics for prospective ADHD outcomes. Only a minority of variables may have potential predictive value for predicting ADHD outcomes, beyond baseline behavior, with moderate (non-neurocognitive) to small (neurocognitive) effects. A person-based neurocognitive profiling approach yet seems most promising, although the predictive power of these subgroups is also limited (yet). The often absent relationship between neurocognitive functioning and ADHD outcomes not only has consequences for our search to variables that may help inform us on prognostic perspectives, but also has important meaning for several models on neurocognitive functions in ADHD. On the other hand, person-based neurocognitive profiling approaches may be a more important direction in future studies.

Implications for Models in ADHD

The mainly absent or weak relationship between neurocognitive functioning and ADHD outcomes not only has consequences for our search to variables that may help inform us on prognostic perspectives, but also has important meaning for the several models on neurocognitive functions in ADHD that were mentioned in the Introduction section. See Figure 7.1 for a visual overview together with a summary of results that fit each model.

The remarkable absent relationship between neurocognitive functions and ADHD outcomes in children that already have an ADHD diagnosis leads us to suggest that, at least once ADHD has set on, neurocognitive deficits are not directly related to the further course of ADHD symptoms, i.e. do not lie in the causative chain, as was commonly thought based on cross-sectional findings. Instead, our findings point into the direction that neurocognitive functions may act as epiphenomena, perhaps being related to the same underpinnings as ADHD symptoms but not causally related. Such a model also accounts for the inconsistencies that were observed regarding controls and unaffected siblings having an inaccurate slow neurocognitive profile, or children with ADHD having an overall average or fast and accurate profile. Such an epiphenomenal model is in line with other studies that, for example, showed that persistent genetic factors underlie the longitudinal relationship between ADHD and intelligence in twins (Rommel, Rijsdijk, Greven, Asherson, & Kuntsi, 2015), or found shared genetic etiology between several neurocognitive functions (e.g. memory, reaction time speed, reasoning abilities), and psychiatric symptoms (Hagenaars et al., 2016).

However, we think it may be premature to firmly conclude at this point that neurocognitive functions are not causally related to the disorder, as we also concluded that using longitudinally informed neurocognitive subgroups led to a different pattern of outcomes (**chapter 6**). Findings thus may depend on methodological aspects (e.g. which measures are included, which approach [person-based versus a group-mean approach] is used), which is also relevant to the limitation (see further) that we did not (thoroughly) investigated the domain of reward processing and cognitive control. Although evidence best fit an epiphenomenal model so far, the option of an endophenotypic role of neurocognitive functions is not fully excluded, especially as the neurocognitive subgrouping approach did appear to identify a 'risk' profile, and working memory and reaction time variability showed up as baseline predictors for future outcomes. It is therefore of importance to further explore such person based approaches and/or the role of working memory and reaction time variability to draw more firm conclusions.

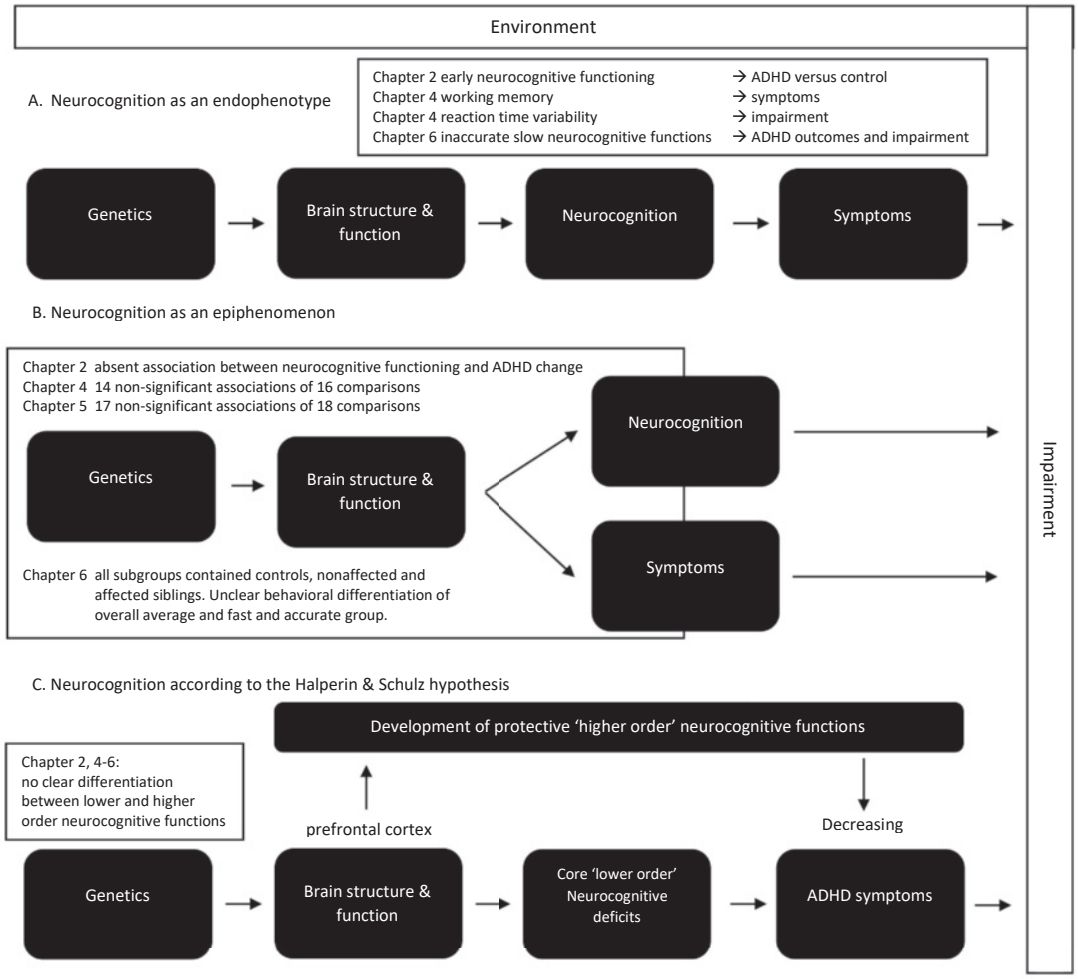

Figure 7.1. Visual summary of different models that included neurocognitive functioning in pathways to ADHD. Figure 7.1A and 7.1B are inspired by Coghill et al., 2014. 'Environment' refers to bi-directional relationships with all levels in the pertinent models.

Of interest are the differential findings from this thesis regarding predicting the onset of ADHD (for example early neurocognitive functions predicted ADHD in childhood – **chapter 2**; or being at risk for late onset ADHD with an inaccurate slow longitudinally informed profile – **chapter 6**) and predicting the further course of ADHD. Speculating on this, there may be a role for neurocognitive functioning in the prediction of the onset of ADHD, while neurocognitive functioning may not be clearly involved in the prediction of full ADHD remittance. Such a differentiation between onset and further course of the disorder is confirmed by multiple studies demonstrating that neurocognitive functioning in general may relate to the emergence or existence of ADHD in young children (Pauli-Pott & Becker, 2011; Rajendran, Rindskopf, et al., 2013; Sjöwall et al., 2015; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013), but is not clearly related to the course of ADHD (Coghill et al., 2014; McAuley et al., 2014; Miller, Ho, & Hinshaw, 2012; van Lieshout et al., 2013). Additionally, such a differentiation is also supported by studies reporting that particular genetic factors are involved in the onset of ADHD, and that other genes contribute to persistence or remittance of ADHD (Chang, Lichtenstein, Asherson, & Larsson, 2013; Pingault et al., 2015). Perhaps in younger years neurodevelopmental factors have a larger impact, while with aging more and more other (interrelated) factors may impact on pathways to behavior, such as parenting styles, peer relationships, school performance/failure, self-esteem and so forth (Sonuga-Barke & Halperin, 2010). This thus may suggest that remittance of ADHD is far more difficult to predict and may be impacted by many more and other variables compared to the early onset of ADHD.

Further speculating, it may be well possible that our biological system is very multifaceted with several models in play, being complexly intertwined and overlapping. This may lead us to keep finding different, inconsistent or unexpected findings. For example, next to the epiphenomenal and endophenotypic models that we discussed yet, it may be also possible that ADHD has certain neurocognitive deficits as a consequence, perhaps as a result of person-environment interaction (Coghill et al., 2005); e.g. a person with ADHD may search for a different environment (less nuisance, quiet, or stimulus-rich, etc), and that environment may impact on (the expression of) neurocognitive (dys)functioning. One study yet demonstrated that both ADHD symptoms and neurocognitive functioning related to ADHD symptoms and neurocognitive functioning at follow-up (Rajendran, Rindskopf et al., 2013).

Taken together, findings from the current thesis best fit the idea that neurocognitive functioning and ADHD symptoms may be related to each other through common underlying mechanisms instead of being directly causally related, at least in relation to the further course of the disorder. Onset of ADHD (or ADHD at an early age) may be better to predict. However, we also have discussed that causality (at least in some way), or other more complex models, cannot be fully ruled out.

Clinical Implications

Our findings add to the current idea that ADHD is not only a childhood disorder (Klein et al., 2012), but rather is a disorder that lasts into (young) adulthood for many affected individuals. Relating to the debate that ADHD may be over-diagnosed (Ford-Jones, 2015), an important difference with clinical practice is that diagnostic outcomes in this study were of no interest to families nor assessors: Diagnostic outcomes were not linked back, had no specific consequences for school or treatment indications, for example. Therefore, we consider our diagnostic assessment as objective as possible – acknowledging the challenges that exist concerning behavioral classifications based on more or less arbitrary cut-off points, as no real objective marker of ADHD is known at this point. With our effort to objectively and extensively investigate diagnostic information over time, we can acknowledge that once affected, problems are clearly not dissipated but likely (partially) continue into adolescence or young adulthood.

Based on the strong persistence of ADHD and related problems, it may clinically be important to follow-up and treat children/adolescents with ADHD, to decrease the burden from this disorder. This argues for a further effort into defining what the best way of support or treatment during the course of this disorder is, on which we will speculate a bit further now, noting that this was not the topic of our investigation. Our findings do not provide evidence for an important role for pharmacological treatment. The amount of pharmacological treatment did not seem to contribute to better outcomes in our sample and may have aversive side effects, which was in line with findings from another studies (Langberg & Becker, 2012; Molina et al., 2009; van de Loo-Neus, Rommelse, & Buitelaar, 2011). Speculating on alternative ways of treatment, another thought may be that training of neurocognitive functions may be valuable (Titz & Karbach, 2014, but for a contrasting view please see Rapport, Orban, Kofler, & Friedman, 2013). This may seem a counterintuitive thought given the fact that associations with ADHD and overall functioning in this thesis are weak (consistent with findings that training specific neurocognitive functions may not directly lead to improved ADHD behavior, Rapport et al., 2013). However, strengthening or compensating deficits in neurocognitive functions may increase particular domains of functioning next to ADHD behavior (Tucha et al., 2011): For example, when improving the ability to direct and maintain attention to the outer world, this may lead to improved social skills as one could better/longer listen and respond to peers or parents, which may in turn lead to improved quality of relationships. In addition, mindfulness-based interventions aim to enhance attention and to reduce harsh self-judgments, which may lead to more optimal functioning (Semple, Lee, Rosa, & Miller, 2010). Indeed, it has been shown that such intervention programs, including both the parents and the children, may lead to improved behavioral functioning as reported by the parents and children themselves (Semple et al., 2010; van der Oord, Bogels, & Peijnenburg, 2012). Summarizing, monitoring and

treatment may clinically be important in (persistent) ADHD, and there is some evidence to suggest that - even when neurocognitive functions are not causally related to ADHD symptoms - it may be that neurocognitive training may lead to improved functioning in specific areas, perhaps increasing an individual's wellbeing.

By investigating neurocognitive functions our goal was to increase the percentage of explained variance in terms of behavioral outcomes. However, we found only meager evidence that neurocognitive functions measured at one point in time would prove useful as prognostic factors. Even when detecting significant predictors (e.g. working memory and reaction time variability), these predictors only had small effect sizes. Using a person-based neurocognitive profile analysis yet had the largest predictive value, with small to moderate effect sizes regarding the differentiation of the inaccurate slow versus the other two subgroups. Separate from the theoretical model that our findings may fit, it seems that the clinical value of neurocognitive functions as predictors for the further course in yet affected children is limited at this point. In terms of clinical applicability, our findings most specifically indicate that an overall weak neurocognitive profile is reason for concern, since it is a less common phenomenon in control children, increases the odds for (a persistent form of) ADHD, and may (tentatively) index a risk for late onset ADHD in children at familial risk for ADHD. However, as such findings are not specific to ADHD (e.g. having an overall weak profile is not exclusively reserved for affected children), such a profile could only be used as a careful indicator of a larger risk of a worse prognosis. As it is well possible that behavioral (ADHD) outcomes are the sum of many different minor (interacting) effects, which are not yet clinically available, it could be suggested that neurocognitive functioning may have a modest place in clinical practice at this point.

Strengths and Limitations

Findings in this thesis should be viewed in the light of its strengths and limitations. Specific strengths are the longitudinal design in which a relatively large battery of identical neurocognitive measures was included at two timepoints. We were able to investigate a relatively large sample including the full spectrum of ADHD symptoms, thereby taking into account potential confounding effects of age, gender, and pharmacological treatment. Further, an extensive diagnostic assessment, in which different types of instruments (e.g. clinical interview, supplemented with questionnaires) were used in order to establish a thorough DSM-diagnosis. In addition, the course of ADHD and its neurocognitive characteristics was investigated over a six year interval, which is larger than that in many other studies (Brocki, Nyberg, Thorell, & Bohlin, 2007; Kalff et al., 2005; Kalff et al., 2002; Vaughn et al., 2011) and would enable children to enter a new developmental phase.

Although we undertook considerable effort to perform an optimal study, some limitations should be noted as well. First, some aspects of our sample limit generalization to the (ADHD) population, including (1) our exclusive focus on individuals with combined type ADHD, (2) the limited representation of girls in our sample – although the results did not change when taking gender into account -, (3) the inclusion of only Caucasian participants, (4) including children with a clinical ADHD diagnosis instead of children from the general population, and finally (5) including children with ADHD that were mostly medicated; having a 48-out wash-out period may not be enough to account for the more structural impact of medication (Spencer et al., 2013); however, grossly, our findings indicate that pharmacological treatment did not change results. Second, our findings may not be generalized to other neurocognitive domains, such as reward related neurocognitive functions or other cognitive control functions beside working memory. In addition, we were not able (except in chapter 4) to measure a neurocognitive construct based on multiple measures, which would have increased reliability. However, we have chosen not to increase the testing burden for our participants, which consequently may have resulted in fatigue and data loss due to drop outs which would impact on the quality of our data. Third, we have chosen to use performance-based measures of neurocognitive functioning. Rater-based measures of neurocognitive functioning may show higher predictive value, as these measures may be more closely related to behavior and investigate capacities in more unstructured situations, which may better mirror 'real-life' functioning (Toplak, West, & Stanovich, 2013). Fourth, regarding questions of causality: although we performed a longitudinal study, which may be valuable in unraveling patterns of causality to a certain extent given the fact that one may order relationships in time, this does not equal an experimental design. Fifth, regarding the discussion on the endophenotype model (or others), we did not investigate all criteria set forth for the endophenotypic characteristics of neurocognitive functions as for example described by Gottesman & Gould (2003). Finally, most participants with ADHD at outcome already had the diagnosis at baseline which led us to focus specifically on how behavioral and neurocognitive patterns may be (causally) related in the *course* of the disorder, which may be different from mechanisms regarding the *onset* of ADHD. Our conclusions regarding the latter point thus are more tentative.

Future Research

The current thesis has addressed specific questions regarding the course of, and relationship between ADHD symptom severity and neurocognitive functioning. This has led to the emergence of new questions and recommendations for future studies.

To further disentangle the complex relation between neurocognitive functioning and ADHD symptoms specifically, future studies preferably should start as large (or representative sub-) population samples in very young children, when the full expression of ADHD has yet to set. From there on the relationship between neurocognitive functioning and ADHD symptomatology should be investigated bidirectionally at multiple points in time, into adulthood. In that way, associations between neurocognitive functioning and the onset as well as the further course/remission of ADHD, can be studied in greater detail. In addition, our findings suggest that it is important to further define more homogeneous subgroups in ADHD, for example based on neurocognitive performance or creating subgroups based on both neurocognitive and behavioral information. Adding key neurocognitive functions such as reward processing, cognitive control (Sonuga-Barke, Bitsakou, & Thompson, 2010), but also adding other functions for example capturing social cognitive functioning may add to a more complete understanding of ADHD and the relationship with neurocognitive functions.

Another point is that future studies are recommended to target domains besides specific DSM-based ADHD diagnoses or symptoms, as investigating ADHD symptomatology itself is a narrow way of looking into an individual's wellbeing. The importance of the use of the DSM is obviously that we have nosologically agreement on several types of problems, and with that, it is yet a vital instrument in both clinical practice and research. By including a measure that captures several domains of overall functioning (psychological, academic, social) we have made a first attempt to look beyond ADHD symptoms, however, this clearly should be extended much further. An interesting view that goes beyond the DSM is the network approach as described by Borsboom and colleagues (2017), that tenets that mental disorders arise from (causal) interactions between varying symptoms of psychopathology and biological, psychological and societal mechanisms, within one network. This could be seen as a more transdiagnostic approach to conceptualizing psychopathology. Perhaps, neurocognitive functions could be of value in such a network approach. In addition, we consider it very likely that by "including" six years of time in the prediction models, a lot of 'nuisance' is added; for example in the form of (epi-)genetic variations that may differ over time (Chang et al., 2013), but also the large amount of environmental variations and its interactions. Future studies thus preferably should include other variables, such as those relating to family-environmental factors. For example, studies have shown that chaotic home environments (Evans, 2006; Martin, Razza, & Brooks-Gunn, 2012), upbringing style (Morrell & Murray, 2003), attachment style (Richards, 2013), or family relationships (defined by parental expressed emotions, e.g. maternal warmth, maternal criticism; Richards et al., 2014), are associated with poorer developmental outcomes (e.g. academic, socio-emotional, behavioral, or self-regulatory abilities).

In this regard, it is worth mentioning that The National Institute of Mental Health (NIMH) has introduced a very promising extensive project in which such a transdiagnostic view is taken, acknowledging the complexity of psychopathological mechanisms in the context of developmental and environmental aspects. With the Research Domain Criteria project (RDoC, see https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml for further details), a framework for research on psychopathology (e.g. genomics and neuroscience) is created (Insel et al., 2010). This framework is centered around five dimensional psychological constructs that are relevant to human behavior and mental disorders; negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems, which are studied on several levels, e.g. genetic, molecular, neurobiological, behavioral. Ultimately, world-wide data-collection and collaboration in such an extensive framework would further increase our knowledge on general psychopathology and pathophysiology and specifically ADHD related behavioral problems, in which neurocognitive functioning may act as one part of this enigma. Consequently, the scientific system also may benefit from larger and better cooperation across study groups, countries and continents. In the end, such an extensive approach will guide treatment development, selection and planning in much greater detail than we have available yet, thereby optimizing an individual's wellbeing together with his social system.

Key Findings & Conclusions

* ADHD/C is largely persistent into adolescence and young adulthood on the dichotomous level (diagnosis yes/no), with a slight ADHD symptom decrease on the continuous level.

* In terms of persistence of neurocognitive functioning: Verbal working memory, reaction time variability and intelligence remain impaired in affected and unaffected siblings when reaching adolescence and young adulthood compared to controls.

* Several other neurocognitive functions in both affected and unaffected siblings trend to (time reproduction, time production variability, reaction time speed), or fully catch-up (time production, motor control, aggregated neurocognitive functioning) with control performance levels.

* Following these behavioral and neurocognitive findings, the course of ADHD is unlikely to be fully explained by a maturational delay.

* In terms of predictors, non-neurocognitive variables such as ADHD symptom severity, parent-reported impairment, parental ADHD status and age are valuable predictors for prospective ADHD symptom severity and overall functioning.

* Few neurocognitive variables predict prospective ADHD outcomes: Working memory and reaction time variability predict prospective ADHD symptom severity and overall functioning respectively, over and above behavior, to a small extent.

* Predicting ADHD outcomes (over and above baseline behavior) using neurocognitive change on a group-level reveals no evidence for a relationship between those two variables.

* There is no convincing evidence for a differentiation in lower versus higher order neurocognitive functioning differentially involved in the onset versus the further course of the disorder.

* Three quantitively distinct longitudinally stable neurocognitive subgroups exist in individuals with and without ADHD. A developmentally stable overall weak profile is related to the worst ADHD outcomes.

* Clinically, particularly an overall weak neurocognitive profile may carefully be used as an indicator of a larger risk of worse prognosis next to behavioral factors.

* Further, findings suggest that the clinical value of neurocognitive predictors for prospective ADHD outcomes remains small yet.

* Moreover, findings best fit the suggestion of neurocognitive functions being epiphenomena instead of being a causative factor in ADHD, or indicate more complex models. It is possible that different mechanisms on the onset versus the persistence of ADHD exist.

* A broader network-model in which both ADHD symptoms together with other (comorbid) symptoms and level of functioning should be modelled, in relation to several potential pathophysiological mechanisms which may include neurocognitive functioning, preferably over time and in relation to environmental interactions.

Table 7.1. Summary of the main findings of this thesis

Chapter	Participants	Baseline measures	Follow-up measures	Main findings
2	Review: 18 studies	*Predictor* ▪ Cognitive control ▪ Reward processing ▪ Timing ▪ Alerting attention ▪ Orienting attention ▪ Intelligence ▪ Visual information processing speed ▪ Basic information processing speed	*Predictor* ▪ Cognitive control ▪ Timing ▪ Alerting attention ▪ Intelligence ▪ Basic information processing speed *Outcome* ▪ ADHD status - Symptom severity - Symptom change - Diagnosis - Persistence	▪ ADHD persisters and remitters could not be differentiated based on (higher or lower order) neurocognitive functions ▪ Both ADHD persisters and remitters had weaker neurocognitive performance than controls ▪ Neurocognitive functions in (young) childhood predicted ADHD a few years later
3	347 children with ADHD/C Baseline age: 5-19 years	*Predictor* ▪ Demographics (Age, sex SES) ▪ ADHD familiality (% siblings with ADHD, current parental ADHD) ▪ ADHD characteristics (ADHD symptoms, impairment, age of onset) ▪ Comorbidities (ODD, CDD, mood/anxiety) ▪ Pharmacological treatment	*Outcome* ▪ ADHD status - Symptom severity - Symptom change - Persistence ▪ Comorbidities ▪ Overall functioning ▪ Pharmacological treatment	▪ Majority of participants persisted in ADHD diagnosis (87.5%). Only 5.1% fully remitted at follow-up ▪ Comorbidities decreased strongly ▪ Pharmacological treatment (taken at any time) increased ▪ About half of participants were still functionally impaired at follow-up ▪ Baseline predictors parental ADHD, higher ADHD symptom severity and more impairment positively predicted prospective ADHD symptom severity ▪ Baseline predictors (younger) age, higher ADHD symptom severity, and more impairment positively predicted

		(use of psychostimulants until baseline/until follow-up)		prospective overall functioning ▪ Pharmacological treatment had no (beneficial) impact on either symptom severity or impairment
4	226 children with ADHD/C Baseline age: 5-19 years	*Predictor* Component scores in eight domains: ▪ Working memory ▪ Motor inhibition ▪ Cognitive inhibition ▪ Reaction time variability ▪ Timing ▪ Reaction time speed ▪ Motor control ▪ Intelligence	*Outcome* ▪ ADHD symptom severity ▪ Overall functioning	▪ In general, only few neurocognitive domains appeared to have predictive value: ▪ Better working memory at baseline predicted lower prospective ADHD symptom severity ▪ Less reaction time variability at baseline predicted better prospective overall functioning ▪ These predictors remained valid with baseline behavioral measures included in the models
5	339 children with ADHD/C 271 unaffected siblings 228 controls Baseline age: 5-19 years	*Predictor* ▪ Overall measure of neurocognitive functioning (aggregated score) ▪ Verbal working memory ▪ Time production ▪ Time reproduction ▪ Reaction time variability ▪ Time production variability ▪ Reaction time speed ▪ Motor tracking control ▪ Intelligence	*Predictor* ▪ Overall measure of neurocognitive functioning (aggregated score) ▪ Verbal working memory ▪ Time production ▪ Time reproduction ▪ Reaction time variability ▪ Time production variability ▪ Reaction time speed ▪ Motor tracking control ▪ Intelligence	▪ Both affected and unaffected siblings trended to, or fully caught up with controls on about half or the neurocognitive measures ▪ Performance on remaining key neurocognitive domains (verbal working memory, timing variability) remained impaired at follow-up in both groups ▪ Change in neurocognitive functioning was not related to ADHD outcomes

			Outcome ▪ ADHD symptom severity ▪ Overall functioning	
6	200 children with ADHD/C 147 unaffected siblings 171 controls Baseline age 5-19 years	*Predictor* ▪ Verbal working memory ▪ Time production ▪ Time reproduction ▪ Reaction time variability ▪ Time production variability ▪ Reaction time speed ▪ Motor pursuit control ▪ Motor tracking control	*Predictor* ▪ Verbal working memory ▪ Time production ▪ Time reproduction ▪ Reaction time variability ▪ Time production variability ▪ Reaction time speed ▪ Motor pursuit control ▪ Motor tracking control *Outcome* ▪ ADHD symptom severity ▪ Comorbid problems - Oppositional behavior - Anxious-shyness - Social problems ▪ Overall functioning ▪ ADHD course - Symptom change - Persistence/remittance	▪ LCA revealed three quantitively distinct developmentally stable neurocognitive subgroups - 1: inaccurate slow - 2: overall average - 3: fast yet accurate ▪ The inaccurate slow subgroup has the worst outcomes at follow-up (ADHD symptoms, overall functioning, oppositional behavior, social problems), and may index a risk for late onset ADHD in children with familial risk. ▪ All subgroups contained ADHD (un)affected siblings and controls, indicating limited specificity of the subgroups

Note: Table 7.2 describes instrument names of variables that are mentioned in the current Table (7.1). ADHD = Attention-Deficit/Hyperactivity Disorder; ADHD/C = ADHD Combined subtype; CD = Conduct disorder; LCA = Latent class analysis; ODD = Oppositional Defiant Disorder; SES = socioeconomic status.

Table 7.2. Overview of specific instruments

ADHD behavioral measures	Baseline	Follow-up
ADHD diagnosis	PACS interview with parents, establishing an DSM-IV-TR diagnosis using an extensive algorithm	K-SADS interview with parents, and with child ≥ 12 years, establishing a DSM-5 diagnosis using an extension algorithm.
ADHD symptom severity	CPRS-R:L	CPRS:R-L
Impairment	SDQ (parent report)	
Overall functioning		K-GAS score
Neurocognitive predictors/variables		
(Verbal) working memory	Digit Span Task	Digit Span Task
	Visuo-spatial Sequencing Task[a]	
Motor inhibition	Stop Task[a]	
Cognitive inhibition	ANT Shifting Attentional Set, block 2[a]	
Reaction time variability	ANT Baseline Speed	ANT Baseline Speed
	ANT Shifting Attentional Set, block 1[a]	
	Stop Task[a]	
	Motor Timing Task[a,b]	
Timing variability	Motor Timing Task	Motor Timing Task
Timing	Motor timing	Motor timing
	Time Test	Time Test
Reaction time speed	ANT Baseline Speed	ANT Baseline Speed
	ANT shifting attentional set, block 1[a]	
	Stop task[a]	
Motor control	ANT Pursuit[c]	ANT Pursuit[c]
	ANT Tracking	ANT Tracking
Intelligence	WISC/WAIS-III four subtests	WISC/WAIS-III two subtests
Other predictors/variables		
Age	Based on birth date and testing date	Based on birth date and testing date
Sex	Demographics questionnaire	Demographics questionnaire
SES	Demographics questionnaire	
ADHD familiality	PACS ADHD diagnosis	K-SADS ADHD diagnosis
Age of onset	Derived from PACS interview	
ODD, CD	Derived from PACS interview, DSM-IV based	Derived from PACS interview, DSM-IV based
Mood/anxiety	Derived from PACS interview, screening score	Derived from K-SADS interview, DSM-IV based
Tic disorders		Derived from K-SADS interview, DSM-IV based

Pharmacological treatment	Cumulative intake of psychostimulants in months until baseline measurement	Cumulative intake of psychostimulants in months until follow-up measurement
Social problems		CPRS-R:L
Anxiety/shyness		CPRS-R:L
Oppositional behavior		CPRS-R:L

Note: ADHD = Attention-Deficit/Hyperactivity Disorder; ANT = Amsterdam Neuropsychological Tasks ;CD = Conduct disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long version; DSM-IV-TR = Diagnostic and Statistical Manual of mental disorders (4th edition, text revision); K-GAS = Global Assessment Scale-score of the K-SADS; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia for school-age children; ODD = Oppositional Defiant Disorder; PACS = Parental Account of Children's Symptoms; SDQ = Strengths and Difficulties Questionnaire; SES = socioeconomic status; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler intelligence Scale for Children.

[a] This task is investigated only in chapter 4. [b] Variability on the Motor Timing Task was used to compose a component score named reaction time variability in chapter 4, and as a separate timing variability measure in chapter 5 & 6. [c] This task is investigated in chapter 4 and 6.

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Nederlandse Samenvatting

Summary in Dutch

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD), of aandachtstekortstoornis met hyperactiviteit in het Nederlands, is een veel voorkomende psychiatrische ontwikkelingsstoornis. Zo'n 5% van de kinderen en jongeren heeft een diagnose ADHD (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014), alsmede ongeveer 2.5% van de volwassenen (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). ADHD wordt gekenmerkt door een mate van aandachtsproblemen en/of hyperactiviteit en impulsivitieit die niet past bij de leeftijd, en die tot beperkingen in het functioneren leidt; bijvoorbeeld binnen het gezin, op school/werk, in sociaal opzicht. Er kunnen drie symptoompresenties worden onderscheiden; ADHD met overwegend aandachtsproblemen, ADHD met overwegend hyperactiviteit/impulsiviteit en tot slot ADHD met zowel aandachtsproblemen als hyperactiviteit/impulsiviteit, de gecombineerde presentatie. Veel individuen met ADHD hebben vaak ook nog een andere (comorbide) diagnose, zoals een oppositionele gedragsstoornis of een stemmingsstoornis (Gillberg et al., 2004). Het is goed voorstelbaar dat het hebben van meerdere psychische of gedragsproblemen het functioneren nog verder kan beperken.

Het lagere prevalentiecijfer van ADHD bij volwassenen ten opzichte van kinderen en jongeren doet vermoeden dat er sprake is van een leeftijdsgebonden afname van symptomen. Een literatuurstudie hiernaar wees inderdaad uit dat bij kinderen met ADHD, vanaf het negende levensjaar de mate van ADHD (diagnose) elke vijf jaar afneemt met 50% (Hill & Schoener, 1996). De symptomen van hyperactiviteit en/of impuslviteit nemen het sterkst af, terwijl aandachtsproblemen relatief stabiel blijven met het ouder worden (Biederman, Mick, & Faraone, 2000). De manier waarop men persisterende (aanhoudende) ADHD definieert is hierbij (uiteraard) wel van belang. Een volwaardige op de *Diagnostic and Statististic Manual of psychiatric disorders* (DSM) gebaseerde diagnose leidt tot lagere persistentie cijfers dan ADHD die gedeeltelijk al herstellende (in partiele remissie) is, terwijl ook bij die laatste vorm vaak nog beperkende symptomen aanwezig zijn (Faraone, Biederman, & Mick, 2006). Verschillende studies samennemend blijkt dat een groot deel van de kinderen persisterende en beperkende symptomen van ADHD heeft in de jonge volwassenheid (zie bijvoorbeeld Faraone et al., 2015).

De vraag hoe ADHD nu precies 'ontstaat' is er één die nog moeilijk te beantwoorden is. Het is waarschijnlijk dat ADHD het resultaat is van een complex samenspel tussen genetische, neurobiologische (zoals hersenstructuren of functioneren van breinnetwerken), neurocognitieve (de meer 'zichtbare' output van het brein, zoals functioneren van het [werk]geheugen, aandachtsspanne, mogelijkheid tot remming van of flexibel schakelen in gedrag, zie ook verderop) en omgevingsfactoren (Faraone et al., 2015; Faraone et al., 2005). Zo wordt de erfelijkheid van ADHD in tweelingsstudies geschat rond de 76% (Faraone et al., 2005). Voorts is gebleken dat

dit op zichzelf al een complex samenspel is van vele genetische factoren, die interacteren met de omgeving, en die elk overwegend een klein effect hebben. Vermoedelijk zijn er verschillende genen betrokken bij verschillende ontwikkelingsfases, mogelijk gerelateerd aan zowel het ontstaan als het verdere beloop van ADHD (Chang, Lichtenstein, Asherson, & Larsson, 2013; Pingault et al., 2015). Tevens zijn er verschillende specifieke omgevingsfactoren die gerelateerd lijken aan ADHD (zie bijvoorbeeld Thapar, Cooper, Eyre, & Langley, 2013). Zo komen extreme vroege moeilijkheden (denk aan extreme deprivatie), pre- en postnatale blootstelling aan lood en een laag geboortegewicht/prematuriteit vaker als risicofactor voor ADHD naar voren. Echter kun je in deze gevallen niet duidelijk spreken van oorzaak-gevolg, aangezien het (zeer goed) mogelijk is dat associaties op hun beurt weer samenhangen met genetische aanleg, of voortkomen vanuit een derde (onbekende) variabele. Al met al geeft het mogelijke samenspel tussen genetische en omgevingsfactoren vele mogelijkheden voor het tot uiting komen van ADHD gerelateerde symptomen. Er wordt vaak gedacht dat genetische aanleg in combinatie met omgevingsfactoren tot specifiek gedrag leiden, via (onder andere) (dysfunctionele) brein netwerken. Daarmee zijn neurobiologische en neurocognitieve factoren tevens interessant om te bestuderen. Op de neurocognitieve factoren wordt verderop nader ingegaan. Ten aanzien van neurobiologische variabelen kan grofweg gezegd worden dat veel studies hebben aangetoond dat er verschillen zijn in bepaalde hersenstructuren en/of functioneren tussen kinderen en volwassenen met ADHD en niet aangedane individuen (zie bijvoorbeeld voor een overzicht Cortese et al., 2012). Belangrijk is hierbij om te noemen dat er grote verschillen zijn bínnen de groep individuen met ADHD en daarnaast is er overlap tussen de groepen mét en zonder ADHD. Al met al lijken verschillende factoren op verschillende 'niveaus' een bijdrage te leveren aan het ontstaan danwel aan het voortbestaan van ADHD.

De Rol van Neurocognitief Functioneren bij ADHD

In dit proefschrift wordt met de term 'neurocognitief functioneren' verwezen naar psychologische processen die mogelijk maken dat informatie verwerkt wordt, die het resultaat zijn van verschillende biologische processen in het brein. Het is een overkoepelende term voor de kwaliteit van specifieke neurocognitive functies, zoals bijvoorbeeld aandacht, geheugen, leervermogen, die tezamen kunnen leiden tot waarneembaar gedrag, zoals een impulsieve reactie. Bij ADHD vormen neurocognitieve problemen al geruime tijd de kern in verschillende theoretische modellen. Zo werd onder meer gedacht dat een heel specifiek neurocognitief problem onderliggend was aan het tot uiting komen van ADHD, door problemen met de uitvoerende (executieve) functies (Barkley, 1997). Later werd gepostuleerd dat de stoornis te maken heeft met drie belangrijke neurocognitieve disfuncties die afzonderlijk of in combinatie met elkaar een rol kunnen spelen: problemen met de

cognitieve controle, problemen met de verwerking/gevoeligheid van beloning, en/of problemen met het verwerken van temporele informatie (bijvoorbeeld het inschatten van een tijdsinterval); zie bijvoorbeeld Sonuga-Barke, Bitsakou, & Thompson, 2010. Een meer recente ontwikkeling is dat gekeken wordt naar specifieke patronen in de prestatie van één individu op verschillende taken/domeinen (sterkte en zwakte), zogeheten neurocognitieve profilering of subgroepering (zie bijvoorbeeld Bergwerff, Luman, Weeda, & Oosterlaan, 2017). Het voordeel van zo'n aanpak is dat je het complexe samenspel van de verschillende neurocognitieve functies onderling bínnen een individu beter in beeld brengt, en op die manier wellicht dichter bij het fundament van de stoornis komt. Enkele studies hebben dit onderzocht en laten zien dat er binnen de groep kinderen met ADHD inderdaad verschillende neurocognitieve subgroepen te onderscheiden zijn. Opvallend daarbij is dat die subgroepen dan niet afhankelijk blijken te zijn van de mate van (ernst van) ADHD symptomen, wat het belang van deze methodiek voor een beter begrip van ADHD overigens juist ondergraaft.

Er zijn een aantal modellen die de rol van neurocognitieve functies wat breder inbedden, en meer holistische beschrijvingen van ADHD geven daarmee. Eén zo'n model is het zogeheten endofenotype model. In dit model wordt de genetica via de neurobiologie, het neurocognitief functioneren, en via omgevingsfactoren gerelateerd aan het 'fenotype', het gedrag. Binnen dit model wordt een causale rol voor neurocognitieve functies verondersteld, namelijk als het zogenaamde endofenotype (zie bijvoorbeeld Gottesman & Gould, 2003) Zo'n endofenotype is een meetbare eigenschap, die zich bevindt op het niveau tussen genen en het gedrag (fenotype) in. Hierbij wordt verondersteld dat het endofenotype dichterbij de betrokken genen van de stoornis (in dit geval ADHD) ligt dan het gedrag zelf, en daardoor mogelijk meer informatie zou kunnen geven over betrokken genen. Vanuit dit model kan verwacht worden dat beter neurocognitief functioneren (of een sterkere ontwikkeling van neurocognitieve functies over de tijd) gerelateerd zou zijn aan toekomstige gedragsmatige uitkomsten, en andersom, dat zwakker neurocognitief functioneren (of achteruitgang in functioneren) gerelateerd zou zijn aan slechtere gedragsmatige uitkomsten.

Hierop aanhakend is het relevant een model te vermelden dat zich meer specifiek heeft toegelegd op de rol van neurocognitieve functies in het *beloop* van ADHD. Halperin & Schulz (2006) maken een onderscheid tussen factoren die bijdragen aan het ontstaan van de stoornis, en mechanismen die leiden tot herstel van de stoornis. Zij beschrijven dat ADHD mogelijkerwijs wordt veroorzaakt door een non-corticale (onder meer basale ganglia, cerebellum) neurale dysfunctie die al van jongs af aan aanwezig is, en relatief stabiel aanwezig blijft door de tijd, los van een eventueel herstel van de ADHD symptomen. Vervolgens zou de ontwikkeling van de prefrontale cortex en geassocieerde circuits in de adolescentie en (jong)volwassenheid kunnen compenseren voor de gedragsmatige beperkingen in het functioneren. Volgens dit model zouden de

neurocognitieve problemen die zowel bij individuen met persisterende ADHD als bij individuen met ADHD in remissie aanwezig blijven over de tijd, de kernproblemen zijn voor het tot uiting komen van de stoornis. Voorts zouden individuen met de sterkste ontwikkeling van de zogenaamde hogere orde neurocognitieve functies (functies die een hogere mate van bewuste inspanning vragen, zoals de cognitieve controle functies) beter gaan functioneren (minder ADHD gedrag) in de adolescentie of (jong)volwassenheid ten opzichte van de individuen met een zwakkere ontwikkeling van die hogere orde neurocognitieve functies.

Tegenover dit model van Halperin & Schulz staat het 'maturational lag' model (vertraging in de ontwikkeling), waarbij er van uitgegaan wordt dat individuen met ADHD met de tijd zullen herstellen van hun ADHD symptomen en van hun neurocognitieve beperkingen (zie bijvoorbeeld Berger, Slobodin, Aboud, Melamed, & Cassuto, 2013). De ontwikkeling van kinderen met ADHD is dus niet zozeer *anders* dan die van kinderen zonder ADHD, maar vooral vertraagd. Dit model geeft overigens verder geen indicaties welke etiologische mechanismen dan leiden tot die vertraging en of dat neurocognitieve functies hier een rol hebben.

Er is echter ook evidentie dat neurocognitieve problemen bij ADHD helemaal niet oorzakelijk gerelateerd zijn aan de expressie van ADHD (Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014). Het is ook mogelijk dat neurocognitieve beperkingen beter gezien kunnen worden als een soort comorbiditeit bij ADHD, gerelateerd aan dezelfde onderliggende factoren als ADHD, maar niet noodzakelijk oorzakelijk gerelateerd aan deze stoornis. Neurocognitieve functies zouden daarmee gezien kunnen worden als een zogenaamd epifenomeen. Al met al kan uit bovenstaande afgeleid worden dat er verschillende ideeën en theorieën bestaan over de rol van neurocognitieve functies bij ADHD.

Doel en Studie-opzet

Het doel van dit proefschrift is onze kennis over het beloop van ADHD en de rol van neurocognitive functies hierbij te vergroten. Allereerst wordt beschrijvend in kaart gebracht wat het beloop is van ADHD symptomen (symptoom verandering en ook persistentie van de diagnose), welke comorbide problemen er zijn, wordt er gekeken naar de beperkingen in het functioneren en wordt het beloop van het neurocognitief functioneren in kaart gebracht. Daarnaast wordt een voorspellend perspectief gevolgd waarbij ADHD uitkomstmaten (ernst van ADHD symptomen, symptomverandering, algemeen functioneren en comorbide problemen) worden voorspeld op basis van gedragsmatige en vooral ook neurocognitive kenmerken die gemeten zijn op twee momenten. De resultaten die in dit proefschrift worden beschreven, zijn gebaseerd op

de metingen van het Nederlandse deel van de International Multicenter ADHD Genetics (IMAGE; baseline meting) en NeuroIMAGE (follow-up meting) projecten. Kinderen met ADHD, hun broertjes of zusjes zonder ADHD en controle groep van kinderen zonder ontwikkelingsstoornis. De eerste meting vond plaats toen de kinderen 5-19 jaar waren, waarbij ze zeer uitgebreid werden uitgebreid onderzocht. Gemiddeld zes jaar later werden deze zelfde deelnemers opnieuw uitgebreid getest. Specifieke factoren zoals leeftijd en behandeling met medicatie worden in dit proefschrift ook meegenomen om zodoende de complexe relatie tussen neurocognitief en gedragsmatig functioneren zo goed mogelijk te kunnen onderzoeken, zeker omdat we deze met een interval van ongeveer 6 jaar tussen de twee metingen in bestuderen.

Samenvatting van de Belangrijkste Bevindingen per Hoofdstuk

In **hoofdstuk 2** is systematisch gekeken naar studies gepubliceerd tussen 1990 en 2011, die bestudeerden of neurocognitief functioneren voorspellend was voor latere uitkomsten van ADHD. Achttien studies werden geïncludeerd, en gaven over het geheel aan dat kinderen met een persisterende diagnose ADHD niet konden worden onderscheiden van kinderen met een ADHD diagnose in remissie, op basis van het neurocognitief functioneren, ongeacht het type neurocognitieve functie. In het algemeen presteerden zowel kinderen met persisterende ADHD als kinderen met ADHD in remissie zwakker dan de controlegroep, waarbij het effect wel iets kleiner was voor kinderen met ADHD in remissie. Voorts werd vastgesteld dat neurocognitieve functies die gemeten waren in de vroegere kindertijd, een diagnose of symptomen van ADHD enkele jaren later kan voorspellen, onafhankelijk van het type neurocognitieve functie. De bevindingen passen niet bij het model van Halperin & Schulz (2006), waarin verondersteld wordt dat kinderen met duidelijk afnemende ADHD symptomen een sterkere rijping van meer bewust gecontroleerde neurocognitieve functies zouden hebben.

In **hoofdstuk 3** onderzochten we het beloop van ADHD van de kindertijd/adolescentie naar de adolescentie/jong volwassenheid, en onderzochten we daarnaast een set mogelijke voorspellers for ADHD uitkomsten zes jaar later. Ondanks dat het percentage kinderen met een persisterende ADHD diagnose hoog bleef, en slechts 5% van de deelnemers met ADHD volledig herstelde, werd er ook een duidelijke afname in symptomen van ADHD en andere (gedrags- en stemmings) symptomen waargenomen en was nog maar de helft functioneel beperkt tijdens de follow-up meting. Verder bleek dat het overgrote gedeelte van de deelnemers op een bepaald punt in de tijd wel een keer medicatie (stimulantia) had genomen voor zijn of haar ADHD. De voorspellende variabelen samen verklaarden ongeveer 20% van de variantie in de uitkomstmaten. Hoe ernstiger de ADHD symptomen en hoe meer door de ouder-gerapporteerde beperkingen, hoe ernstiger de ADHD symptomen en hoe

lager het algemeen functioneren zes jaar later. Daarnaast droeg een huidige diagnose van (een van de) ouder(s) bij aan de voorspelling van symptom ernst, en droeg een lagere leeftijd bij aan een lager algemeen functioneren. Medicatiegebruik tot aan de follow-up meting had geen (positief) effect op ADHD uitkomsten of algemeen functioneren. Wel bleek een hogere cumulatieve inname van medicatie tot aan de follow-up meting ernstiger ADHD symptomen te voorspellen, wat mogelijk uitgelegd kan worden doordat deelnemers met ernstiger ADHD wellicht ook meer medicatie gebruiken. Al met al zijn er enkele variabelen die mogelijk aangeduid kunnen worden als risicofactoren voor een ongunstiger beloop van ADHD, echter bleek het grootste gedeelte van de onderzochte variabelen ongerelateerd aan ADHD uitkomsten.

In de literatuurstudie in hoofdstuk 2 werd vastgesteld dat er nog geen studies waren met een tijdsinterval tussen de metingen van langer dan drie jaar, en oudere kinderen (> 12 jaar) niet onderzocht waren. In **hoofdstuk 4** is getracht hier op in te springen door neurocognitieve voorspellers op de baseline meting te onderzoeken in relatie tot ADHD uitkomsten. Acht domeinen werden onderzocht, namelijk werkgeheugen, motorische inhibitie, cognitieve inhibitie, reactietijd variabiliteit, temporele informatieverwerking (bijvoorbeeld tijdsschatting), informatieverwerkingssnelheid, motorische controle en intelligentie. De resultaten toonden dat een beter werkgeheugen op de baseline meting minder ernstige ADHD symptomen voorspelde, en dat minder variabiliteit in de reactietijd voorspellend was voor een beter algemeen functioneren. Het percentage verklaarde variantie was met 3-5.6% echter klein. De variabelen waren significant voorspellend, boven op de voorspellende waarde van gedrag (bijv. ADHD symptomen) ten tijde van de baseline meting. Daarnaast bleken neurocognitieve functies samen met ADHD gedrag nog betere voorspellers vooor ADHD uitkomsten dan modellen met gedrag of neurocognitieve maten alleen. De gevonden resultaten bleken onafhankelijk van leeftijd, geslacht en behandeling met medicatie. Het feit dat slechts enkele neurocognitieve functies in geringe mate voorspellend waren voor ADHD uitkomsten geeft aan dat de rol van neurocognitief functioneren bij de uitkomst van ADHD niet zo duidelijk is als eerder wel gedacht werd. Dat sluit ook aan bij de bevindingen uit hoofdstuk 2.

In **hoofdstuk 5** werd het beloop van de verschillende neurocognitieve functies onderzocht zowel bij deelnemers met ADHD, als bij hun broertjes en zusjes zonder ADHD en bij deelnemers zonder ADHD, de controlegroep. Vervolgens werd gekeken of het beloop van deze neurocognitieve functies op een bepaalde manier zou relateren aan de continue ADHD uitkomstmaten tijdens de follow-up meting. Zowel de deelnemers met ADHD, als hun broertjes en zusjes zonder ADHD bleken op ongeveer de helft van de variabelen tijdens de follow-up meting (bijna) het prestatieniveau van de controlegroep te behalen. Alleen een maat voor temporele informatieverwerking (schatten van een 1seconde-interval), motorische controle en een samengenomen maat voor neurocognitief functioneren trokken volledig bij naar het niveau van de

controlegroep. Hier tegenover stond dat de prestatie op enkele andere belangrijke neurocognitieve maten (verbaal werkgeheugen, variabiliteit in reactietijd, en intelligentie) aangedaan bleef tijdens de follow-up meting. Voorts bleek dat dit beloop van de neurocognitieve functies over het algemeen niet aan de ADHD uitkomsten gerelateerd was, wat suggereert dat een verbetering danwel verslechtering in neurocognitief functioneren niet één op één omgezet kan worden in (ADHD) gedrag. De bevindingen duiden niet duidelijk (alleen) op een vertraging in de ontwikkeling bij ADHD, maar suggereren dat meer complexe modellen nodig zijn als verklaring. Daarnaast trekken de huidige bevindingen de etiologische relatie tussen neurocognitieve beperkingen en ADHD uitkomsten in twijfel. Dat komt wel overeen met de bevindingen uit hoofdstuk 2 en 4.

Omdat de voorspellende waarde van het neurocognitief functioneren beperkt bleek in hoofdstuk 2, 4 en 5, met slechts geringe effectgroottes, werd in **hoofdstuk 6** een meer vernieuwende, persoons-gebaseerde aanpak ingezet, met het idee nog beter rekening te houden met de verschillen in voorkomen van (neurocognitieve problemen bij) ADHD en ontwikkelings aspecten. Via een specifieke analyse werden meer op elkaar lijkende (homogene), en op informatie van twee metingen gebaseerde neurocognitieve subgroepen geidentificeerd. Voorts werd onderzocht of die specifieke neurocognitieve subgroepen gerelateerd zouden zijn aan de ADHD uitkomstmaten. Hiervoor werden ook nu deelnemers met ADHD, de broertjes en zusjes zonder ADHD en deelnemers zonder ADHD, de controlegroep, onderzocht. Op basis van vergelijkbare neurocognitieve maten als in hoofdstuk 5 werden nu drie over de tijd relatief stabiele neurocognitieve subgroepen gevonden. Eén subgroep werd gekarakteriseerd door een algeheel zwakke (inaccurate en langzame) prestatie, een tweede subgroep door een snelle en ook accurate prestatie, en een derde subgroep met een algeheel gemiddeld profiel. Zoals verwacht had de inaccurate langzame subgroep ook de minst goede klinische uitkomsten tijdens de follow-up meting, waarbij deelnemers vaker een ADHD diagnose hadden ten op zichte van de algeheel gemiddelde subgroep en de snelle plus accurate subgroep. Het hebben van een algeheel zwak neurocognitief profiel is daarmee minder gunstig, omdat dit profiel minder vaak voorkomt bij de controle groep; kinderen met dit profiel een verhoogde kans hebben op een aanhoudende diagnose ADHD; en de bevindingen gaven daarnaast enige aanwijzing dat kinderen die nog geen diagnose ADHD hebben maar wel dit zwakkere profiel, iets meer kans hebben op het ontwikkelen van ADHD op een iets latere leeftijd wanneer ze uit een gezin komen waar ADHD in voorkomt. Verder duiden de bevindingen erop dat het algeheel zwakke profiel ten opzichte van de prestaties van de andere subgroepen relatief stabiel blijft over de tijd; er zijn blijkbaar weinig kinderen binnen dit profiel die relatief verbeteren ten opzichte van de andere subgroepen. Mogelijkerwijs zou het invoegen van dit algeheel zwakke profiel in de klinische praktijk bij ADHD als een indicator de acuratesse van de prognose iets verhogen. Verder is het interessant na te gaan of dit profiel inderdaad bruikbaar zou kunnen

zijn voor het bijtijds signaleren van een kwetsbaarheid voor de ontwikkeling van ADHD op iets latere leeftijd, bij broertjes of zusjes van iemand met ADHD.

Implicaties voor Modellen bij ADHD

Al met al duidt het algehele patroon van de bevindingen op een teleurstellend gebrek aan voorspellende waarde van neurocognitieve functies. Slechts een minderheid van de onderzochte variabelen heeft enige potentiele voorspellende waarde, bovenop baseline gedrags kenmerken, met matige (voor de niet-neurocognitieve) en zwakke (voor de neurocognitieve maten) effectgroottes. Een persoons-gebaseerde aanpak met neurocognitieve profilering lijkt nog het meest waardevol, hoewel ook deze subgroepen nog geringe voorspellende waarde hebben (op dit moment).

De opvallend afwezige relatie tussen neurocognitieve functies en ADHD uitkomstmaten bij kinderen die reeds een diagnose ADHD hebben, leidt richting de suggestie dat wanneer ADHD eenmaal aanwezig is, neurocognitieve beperkingen niet direct gerelateerd lijken aan het verdere beloop van de ADHD symptomen. Er lijkt, gezien het nagenoeg ontbreken van een relatie, geen reden te denken aan een oorzakelijk verband, zoals in het eerder beschreven endofenotype model wel wordt verondersteld. De bevindingen duiden er eerder op dat neurocognitieve functies beter omschreven worden als een epifenomeen bij ADHD; mogelijk gerelateerd aan dezelfde onderliggende factoren als de ADHD symptomen, maar niet causaal aan ADHD verbonden. Het bezien van neurocognitieve functies als epifenomeen verklaart ook dat er op sommige punten toch een relatie wordt gevonden tussen ADHD en neurocognitieve functies, en er tegelijkertijd ook kinderen uit de controle groep en niet aangedane broers of zussen zijn die in de inaccurate langzame subgroep zitten maar geen ADHD hebben.

Hoewel de bevindingen in dit proefschrift redelijk eenduidig zijn, is het toch wat voorbarig nu ferm te concluderen dat neurocognitieve functies niet (causaal) gerelateerd zijn aan ADHD. We vonden tegelijkertijd namelijk ook dat het helpt om neurocognitieve subgroepen te detecteren, en twee eerder belangrijk geachte neurocognitieve functies (werkgeheugen en reactietijd variabiliteit) kwamen naar voren als relevante voorspellers. Daarnaast hebben we ook niet alle neurocognitieve domeinen volledig kunnen onderzoeken. Het ligt daarmee voor de hand deze zaken nog verder te onderzoeken, echter leiden de bevindingen van dit proefschrift er wel toe dat dit met meer gematigde verwachtingen zal mogen zijn.

Klinische Implicaties

Onze bevindingen bevestigen de gedachte dat ADHD niet alleen een ontwikkelingsstoornis is, maar dat veel individuen daar zeker tot in de (vroege) volwassenheid beperkingen van ondervinden. Op basis van de hoge mate van persistentie van ADHD en gerelateerde problemen wordt het belang om kinderen en adolescenten met ADHD goed te volgen en wellicht te behandelen verder versterkt. Helaas bleek de mate waarin neurocognitieve functies zouden kunnen dienen als voorspellers van de prognose mager. Daarmee hebben we op dit moment geen heel gerichte handvatten voor de klinische praktijk waarmee kinderen met ADHD duidelijk in een weinig-risico of hoog-risico groep voor zorgelijke uitkomsten zouden kunnen worden ingedeeld. Hooguit kan vanuit de bevindingen afgeleid worden dat het hebben van een algeheel zwak neurocognitief profiel de grootste reden voor bezorgdheid zal zijn. Zo'n profiel is gerelateerd aan een iets hogere kans op een (persisterende) diagnose ADHD. Daarnaast is het, heel voorzichtig gesteld, mogelijk dat bij kinderen met dit algeheel zwakke profiel, waarbij ADHD in het gezin voorkomt, er een iets hoger risico is dat ADHD op iets latere leeftijd nog tot uiting komt.

Ten aanzien van behandeling kunnen we op basis van onze bevindingen, hoewel dit expliciet niet uitgebreid het hoofdonderwerp van studie is geweest, verder nog beschrijven dat er geen evidentie is voor een belangrijke rol van behandeling met medicatie bij ADHD. De hoeveelheid behandeling met medicatie lijkt niet gerelateerd aan betere uitkomsten, en kan nadelige bijwerkingen hebben, wat ook in andere studies werd gevonden (bijvorbeeld Langberg & Becker, 2012, Molina et al., 2009). Ter suggestie voor verdere behandeling kan, ondanks het feit dat er geen tot een zwakke relatie werd gevonden tussen neurocognitieve functies en ADHD uitkomstmaten zelf, mogelijk toch gedacht worden aan het versterken van neurocognitieve functies (Titz & Karbach, 2014). Het versterken of compenseren van neurocognitie(ve beperkingen) kan mogelijk wel specifieke domeinen van functioneren zelf verbeteren (Tucha et al., 2011). Wanneer bijvoorbeeld heel gericht de mogelijkheid de aandacht te richten en behouden op een externe bron versterkt wordt, zou dat kunnen leiden tot verbeterde sociale vaardigheden omdat men beter/langer kan luisteren en interacteren met vrienden of familie. Relaties worden hier mogelijk beter van. Onze bevindingen sluiten dit type effecten niet uit, en daarmee kan het zinvol zijn gericht verder te onderzoeken welke mogelijkheden er zijn voor training van specifieke neurocognitieve functies of vaardigheden.

Toekomstig onderzoek

In dit proefschrift zijn verschillende vraagstellingen rond het beloop van, en de relatie tussen ADHD symptomen en neurocognitief functioneren onderzocht. Dit heeft geleid tot nieuwe vragen alsmede tot aanbevelingen voor toekomstig onderzoek.

Vanwege de gebleken complexiteit aangaande de rol van het neurocognitief functioneren bij ADHD zouden toekomstige studies idealiter starten als grote (of in elk geval representatieve sub-) populatie groepen in zeer jonge kinderen, wanneer ADHD nog echt duidelijk tot uiting moet komen. Vanaf dat moment zouden idealiter zowel neurocognitieve als gedragsmaten op meerdere momenten in de tijd gemeten worden, tot in de volwassenheid. Op die manier kunnen relaties tussen neurocognitief functioneren, aanvang én beloop van ADHD het beste onderzocht worden. De resultaten in dit proefschrift strekken daarbij ook tot de aanbeveling dat meer homogene (op elkaar lijkende) subgroepen worden gedetecteerd, bijvoorbeeld op basis van neurocognitieve prestaties, danwel op basis van neurocognitie en gedrag samen. Voorts kan het bestuderen van in dit proefschrift onderbelicht gebleven belangrijke domeinen zoals verwerking van beloningsgevoelige informatie, of cognitieve controle (Sonuga-Barke, Bitsakou, & Thompson, 2010), maar ook andere neurocognitieve functies zoals sociaal cognitief functioneren bijdragen aan een vollediger begrip van de relatie tussen neurocognitief functioneren en ADHD.

Een tweede type aanbeveling is dat toekomstige studies (uitkomst)maten bestuderen die breder zijn dan ADHD diagnose en symptomen. Deze invalshoek is namelijk sterk gebaseerd op het classificatie gerichte DSM, wat mogelijk te weinig recht doet aan de complexiteit van het gedrag van een individu. Met de maat voor algemeen functioneren hebben we al gepoogd hier een start in te maken, maar het wordt aanbevolen dit verder uit te werken. Hierop aansluitend beschrijven Borsboom en collega's (2017) een zogenaamde 'netwerk' aanpak. Hierin wordt verondersteld dat psychische stoornissen voortkomen uit (causale) interacties tussen verschillende symptomen van psychopathology en biologische, psychologische en sociale mechanismen binnen één netwerk. Zo ontstaat een meer transdiagnostische aanpak voor het begrijpen van psychopathologie. Wellicht dat neurocognitieve functies in zo'n netwerk aanpak, waar mogelijk allerlei kleine effecten tezamen meer van het gedrag kunnen verklaren, van waarde zijn. Verder is het belangrijk dat met een (groot) tijdsinterval, ook anderen nieuwe variabelen hun intrede kunnen doen. Zo is bekend dat (epi-)genetische variabelen verschillende effecten kunnen hebben op verschillende momenten in de tijd (Chang et al., 2013), maar ook de grote hoeveelheid variaties in omgevingsvariabelen en hun interacties. In toekomstige studies zouden neurocognitieve functies, tezamen met allerlei andere type variabelen onderzocht moeten worden, zoals bijvoorbeeld opvoedings- en hechtingsstijlen.

Samenvattend en Concluderend:

- ADHD blijft als diagnose (ja/nee) bij een groot deel van de kinderen met een aanvankelijk geocombineerde symptoom presentatie aanhouden tot ten minste de adolescentie en jong volwassenelheid, waarbij op symptoomniveau een lichte afname waargenomen wordt.

- Het verbaal werkgeheugen, de reactietijd variabiliteit en intelligentie blijven aangedaan in de adolescentie en jonge volwassenheid bij deelnemers met ADHD alsmede bij hun broertjes en zusjes zonder ADHD, in vergelijking met de controle groep.

- Een aantal andere neurocognitieve functies trekken in die beide groepen gedeeltelijk (tijdsschatting reproductie, tijdsschatting productie variabiliteit, reactietijdsnelheid) of geheel (tijdsschatting productie, motorische controle, en algeheel neurocognitief functioneren) bij, tot aan het niveau van de controle groep.

- Deze gedragsmatige en neurocognitieve bevindingen volgend is het onwaarschijnlijk dat het beloop van ADHD alleen en volledig verklaard kan worden door een zogenaamde vertraagde ontwikkeling ('maturational lag').

- In termen van voorspellers voor prospectieve ADHD symptoom ernst en algemeen functioneren blijken de non-neurocognitieve variabelen ADHD symptoom ernst, door de ouder gerapporteerde beperkingen, ouderlijke ADHD status en leeftijd waardevol.

- Slechts enkele neurocognitieve variabelen bleken voorspellende waarde te hebben: werkgeheugen en reactietijd variabiliteit voorspelden respectievelijk prospectieve ADHD symptoom ernst en algemeen functioneren, boven op de gedrasmatige voorspellende waarde, maar met een klein effect.

- Er zijn op groepsniveau geen aanwijzingen dat ADHD uitkomsten aan de hand van neurocognitieve verandering (bijvoorbeeld verbetering) over zes jaar tijd, bovenop het effect van baseline gedragsmaten, voorspeld kunnen worden.

- Er is ook geen overtuigende evidentie voor een onderscheid tussen lagere versus hogere orde neurocognitieve functies die wellicht respectievelijk bij het ontstaan versus het verdere beloop van de stoornis betrokken zouden kunnen zijn.

- Drie kwantitatief verschillende, over de tijd stabiele neurocognitieve subgroepen worden gedetecteerd in deelnemers met en zonder ADHD. Het stabiele algeheel zwakke profiel blijkt daarbij het meest gerelateerd aan de minst goede ADHD uitkomsten.

- In klinisch opzicht lijkt met name het algeheel zwakke neurocognitieve profiel bruikbaar als een indicator voor een groter risico op een slechtere uitkomst, naast gedragsmatige variabelen.
- Verder duiden de bevindingen erop dat de klinische waarde van de neurocognitieve voorspellers voor prospectieve ADHD uitkomsten nog gering is.
- Daarmee lijken de bevindingen het beste te passen bij het idee dat neurocognitieve functies mogelijk beter als een zogeheten epifenomeen beschreven kunnen worden bij ADHD, dan als een oorzakelijke factor, of duiden in elk geval op meer complexe modellen. Ook is het goed mogelijk dat verschillende mechanismen bij het ontstaan versus het verdere beloop van ADHD betrokken zijn.

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About the Author

Including List of Publications

About the Author

Marloes van Lieshout was born on February 14, 1985 in 's-Hertogenbosch. After completing her gymnasium in 2003 (Dominicus College, Nijmegen), she wanted to learn more about human behavior and psychopathology in relation to the brain, neurocognitive functions, and medical conditions. Therefore she obtained her bachelor degree in Neuropsychology and Rehabilitation Psychology (Radboud University Nijmegen, 2006), and her master degree Medical Psychology (Tilburg University, 2008, cum laude). Her thesis focused on the applicability and effects of neurofeedback in patients with Alzheimer's disease in an early stage, studying neurocognitive functioning, mood and behavior. She completed both her thesis and clinical internship at the Department of Medical Psychology of the Catharina Hospital in Eindhoven, and after graduating she has worked there for over half a year. Intruiged by the many questions regarding the development of human behavior in relation to the brain and neurocognitive functioning, she decided to start as a Ph.D. candidate studying behavioral and neurocognitive functioning over time in children and adolescents with and without ADHD; i.e. within the (Neuro)IMAGE study. From 2009-2011, she and her colleages have tested many families with great enthusiasm and care. When data-collection was finished, she felt she wanted to keep in touch with the clinical field. Therefore, in 2012, she took the opportunity to start working as a psychologist at the Vincent van Gogh Centre of Excellence for Neuropsychiatry (Venray), while working on her thesis on a parttime basis as well. In 2014 she could start as a general health care psychologist - in training (in Dutch: GZ-opleiding) at the Vincent van Gogh Institute (polyclinic for addiction care and polyclinic for mood-, anxiety-, and/or personality disorders) and its consortium (De Zorggroep, Venlo), which was completed in 2017. Simultaneously, the result of her scientific interest also has come to an end in the form of this thesis.

Currently, Marloes works as a health care psychologist at a polyclinic and a day-care setting for adults with mood-, anxiety and/or personality disorders at the Vincent van Gogh Institute, in Venray. She challenges her self to efficiently integrate scientific research and knowledge into her clinical work, aiming to improve symptom levels and quality of life of several individuals within a vulnerable period of their life.

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Schweren, L., Hoekstra, P., **van Lieshout, M**., Oosterlaan, J., Lambregts-Rommelse, N., Buitelaar, J., Franke, B., Hartman, C. (2018). Long-term effects of stimulant treatment on ADHD symptoms, social-emotional functioning, and cognition. *Psychological Medicine,* epub ahead of print. doi: 10.1017/S0033291718000545.

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